14 September 2017
EMA/647868/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Adlumiz

International non-proprietary name: anamorelin

Procedure No. EMEA/H/C/003847/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

A/CS	anorexia/cachexia subscale of the FAACT (12-item additional concerns subscale)
AESI	Adverse event of special interest
aLBM	appendicular lean body mass
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
APD	Action potential duration
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
AST	aspartate aminotransferase
ANAM	Anamorelin
AST	aspartate transaminase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the concentration-time curve from time zero to the time of the last measurable plasma concentration
BID	twice daily
BMI	body mass index
BSEP	Bile salt efflux pump
BV	Bioavailability
BW	body weight
C_0	Plasma concentration at time 0
C_{24}	Plasma concentration 24 hours post-dose
CI	confidence interval
CL/F	Apparent total body clearance of drug following extravascular administration
CL_r	Renal clearance as determined by A_{e0-48}/AUC_{0-48}
C_{max}	Maximum plasma concentration
C_{max}/Dose	Dose-normalized maximum plasma concentration
CMO	Contract Manufacturing Organisation
COSY	Correlation Spectroscopy
CPD	Composite Pulse Decoupling
CQAs	critical quality attributes
CrCl	Creatinine clearance
CRS	Chemical Reference Standard
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CV%	Percent coefficient of variation
CYP	Cytochrome P450
DAD	Diode-array detector
DCC	Dicyclohexyl-carbodiimide
DCM	Dichloromethane
DCU	Dicyclohexylurea
DDI	drug-drug interaction
DEPT	Distortionless Enhancement by Polarisation Transfer
DEXA	dual-energy X-ray absorptiometry
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
EM	Extensive metabolizers
EMS	Ethyl Methane Sulfonate
EtOAc	Ethyl Acetate
EWB	emotional well-being (domain/subscale of the FACT-G)
FAACT	functional assessment of anorexia/cachexia therapy (FACT-G + A/CS)
FAACT TOI	FAACT trial outcome index (A/CS + FWB + PWB)
FACIT-F	functional assessment of chronic illness therapy - fatigue (FACT-G + fatigue subscale)
FACIT-F TOI	FACIT-F trial outcome index (fatigue subscale + FWB + PWB)

FACT-G	functional assessment of cancer therapy – general (EWB + FWB + PWB + SWB)
FWB	functional well-being (domain/subscale of the FACT-G)
GC	Gas chromatography
GCP	Good Clinical Practice
GH	growth hormone
GHS-R	growth hormone secretagogue receptor
GI	gastrointestinal
GLP	Good Laboratory Practice
GRLN	G-protein-coupled ghrelin receptor
HAS	hunger assessment scale
HbA1c	Hemoglobin A1c
hERG	Human ether-à-go-go-related gene
HGS	handgrip strength
HPLC	High Performance Liquid Chromatography
Hr(s)	Hour(s)
IC_{50}	Half-maximal inhibitory concentration
ICa	Calcium ion current
ICH	International Conference on Harmonisation
ICV	Intracerebroventricular
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor-binding protein 3
IM	Intermediate metabolizer
IMS	Isopropyl Methane Sulfonate
INa	Sodium ion current
IND	Investigational New Drug
INN	International Non-Proprietary Name
IP	Intraperitoneal
IPA	Isopropanol
IPAc:	Isopropyl acetate
IQR	interquartile range
IR	Infrared
ISS	Integrated Summary of Safety
ITT	intention to treat
IV	Intravenously
KPS	Karnofsky performance status
LBM	lean body mass
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LLOQ	Lower limit of quantification
LS mean	least square mean
MedDRA	Medical Dictionary for Regulatory Activities
MSE	Mean square error term from the analysis of variance
MTD	maximum tolerated dose
N/A	not applicable
NE	not estimable
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NSCLC	non-small cell lung cancer
NSCLC-C	non-small cell lung cancer-cachexia
OAT	organic anion transporter
OATP	organic anion transporter polypeptide
OCT	organic cation transporter
PBO	placebo
PD	Pharmacodynamic(s)
Pgp	P-glycoprotein
PK	Pharmacokinetic(s)
ppm	parts per million
PR	interval from beginning of the P wave to the beginning of the QRS complex
PRO	patient reported outcome
PWB	physical well-being (domain/subscale of the FACT-G)
QD	once daily
QoL	quality of life
QRS	Duration of QRS complex in the frontal plane

QSAR	Quantitative structure-activity relationship
QT	interval from beginning of the QRS complex to end of the T wave in the frontal plane
QTc	Corrected QT
SAE	Serious adverse event
SAP	statistical analysis plan
SD	'standard deviation' or 'single dose'
SE	standard error (of the mean)
SEA	simplified evaluation of appetite (comprises 4 appetite/eating-related questions within the A/CS domain of the FAACT)
SEF	simplified evaluation of fatigue (comprises 4 fatigue/activity-related questions, 3 from the fatigue subscale of the FACIT-F + 1 from PWB subscale of the FACT-G)
SMQ	Standardized MedDRA query
SWB	social/family well-being (domain/subscale of the FACT-G)
$t_{1/2}$	Elimination half-life
TBM	total body mass
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic(s)
T_{max}	Time to maximum plasma concentration
TOI	trial outcome index (see FAACT TOI and FACIT-F TOI)
ULN	upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
XRPD	X-ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Helsinn Birex Pharmaceuticals Ltd submitted on 12 October 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Adlumiz, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2013.

The applicant applied for the following indication:

Treatment of anorexia, cachexia or unintended weight loss in adult patients with non-small cell lung cancer (NSCLC).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that anamorelin (hydrochloride) was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0134/2014 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance anamorelin (hydrochloride) contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 January 2012 and on 24 May 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings Co-Rapporteur: Harald Enzmann

- The application was received by the EMA on 12 October 2015.
- The procedure started on 29 October 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 January 2016.
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 21 February 2016.
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 January 2016.
- During the meeting on 25 February 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The final consolidated List of Questions was sent to the applicant on 26 February 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 September 2016.
- The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Safety andEfficacy assessment of the product:
- GCP inspections were conducted at two clinical investigator sites, one in Russia Federation (between 19 – 22 April 2016) and one in Poland (between 10 – 13 May 2016) and at the CRO site in the USA (between 20 – 24 June 2016). The final integrated inspection report was issued on 25 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 24 October 2016.
- During the PRAC meeting on 27 October 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 10 November 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 January 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 17 February 2017.
- During the CHMP meeting on 23 February 2017, the CHMP agreed on a second list of outstanding issues to be addressed in writing and at an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP second List of Outstanding Issues on 21 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the second List of Outstanding Issues to all CHMP members on 06 April 2017.

- During the CHMP meeting on 21 April 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 18 May 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Adlumiz on 18 May 2017.

1.3. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Eleftheria Nikolaidi

- The applicant submitted written notice to the EMA on 1 June 2017 to request a re-examination of Adlumiz CHMP opinion of 18 May 2017.
- During its meeting on 22 June 2017, the CHMP appointed Johann Lodewijk Hillege as Rapporteur and Eleftheria Nikolaidi as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 17 July 2017 (Appendix 2 of Final Opinion). The re-examination procedure started on 18 July 2017.
- The rapporteur's re-examination assessment report was circulated to all CHMP members on 16 August 2017. The co-rapporteur's assessment report was circulated to all CHMP members on 16 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 1 September 2017.
- During a meeting of the Inter-Committee Scientific Advisory Group (SAG) for Oncology for Adlumiz on 4 September 2017, experts were convened to consider the grounds for re-examination The CHMP considered the views of the SAG as presented in the minutes of this meeting.
- During the meeting on 14 September 2017, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation.

2. Scientific discussion

2.1. Problem statement

Cancer cachexia occurs in more than 80% of patients with cancer before death and is characterized by loss of appetite and/or an aversion to food (anorexia), loss of weight, asthenia, and a poor prognosis. The term “cachexia” refers to a loss of body mass, including lean body mass and fat.

Reduced food intake in patients with cancer is caused by primary anorexia and can be compounded by secondary nutrition impact symptoms. Concurrent hypermetabolism, hypercatabolism and hypoanabolism induced by an abnormal host response to tumour presence and/or tumour factors aggravate the associated weight loss and are provoked by systemic inflammation and catabolic factors

that can act partially via the central nervous system. From a nutritional point of view, this leads to a negative energy and protein balance, manifesting as weight loss.

Cachexia can also have adverse effects on the patient quality of life, as physical activity is impaired by the loss of muscle tissue, concentration and alertness are diminished by fatigue, and mood is dominated by lethargy and increasing indifference.

Often, reduced food intake can be treated through the active management of nutrition impact symptoms (e.g. uncontrolled pain or constipation) or with appetite stimulants or artificial nutritional support. Even though improved nutritional intake can partly reverse fat loss, the metabolic changes resistant to current interventions largely preclude significant reversal of muscle wasting.

No widely approved drug for the treatment of cancer cachexia is available. However, steroid hormones have been shown to be effective in stimulating appetite, with corticosteroids and progestins being more effective than androgens; however, corticosteroids are associated with additional side effects and their positive effects are generally short-lasting.

About the product

Anamorelin is an orally active, high-affinity, selective ghrelin receptor agonist. The gastrointestinal peptide hormone ghrelin is the endogenous ligand for the growth hormone secretagogue receptor (GHS-R), capable of stimulating growth hormone (GH) release from the anterior pituitary gland. Ghrelin acts in the brain to regulate food intake, body weight, adiposity, and glucose metabolism and has therefore the potential to positively affect appetite, energy expenditure, inflammation, adipose tissue and muscle, and ultimately prevent or ameliorate cachexia.

Adlumiz has been developed as an immediate release film-coated tablet containing 100 mg anamorelin HCl intended for administration as a single oral daily dose at least one hour prior to the first meal of the day.

The initially proposed indication for Adlumiz was for the treatment of anorexia, cachexia or unintended weight loss in adult patients with non-small cell lung cancer (NSCLC).

During the evaluation of this application by the CHMP, the applicant proposed to amend the indication to “treatment of anorexia, cachexia or unintended weight loss in adult patients with non-small cell lung cancer (NSCLC) and Body Mass Index (BMI) < 20 kg/m^2.”

The recommnended dose of Adlumiz is 100 mg once daily which should be taken on an empty stomach or at least one hour before a meal.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing 100 mg of Anamorelin hydrochloride (HCl) as active substance.

2.2.2. Active Substance

General information

The chemical name of anamorelin hydrochloride is 2-Amino-N-((R)-1-((R)-3-benzyl-3-(1,2,2-trimethyl-hydrazine-1-carbonyl)piperidin-1-yl)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)-2-methylpropanamide hydrochloride corresponding to the molecular formula $C_{31}H_{42}N_6O_3$•HCl and has a relative molecular mass 583.16 g/mol and has the following structure:

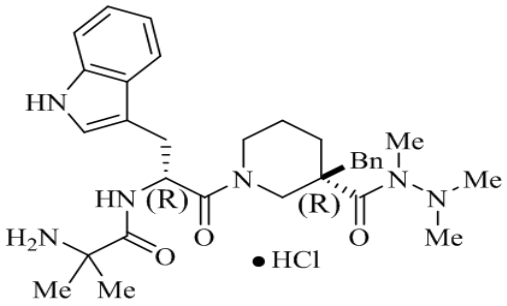


Figure 1. *Structure of anamorelin hydrochloride*

The structure of the active substance was elucidated by a combination of ^{1}H-NMR, ^{13}C-NMR, elemental analysis, FT-IR, UV and and mass spectrometry.

Anamorelin HCl appears as a white to off-white hygroscopic solid, freely soluble in water, methanol and ethanol, sparingly soluble in acetonitrile and practically insoluble in ethyl acetate, isopropyl acetate and n-heptane. Its pka was found to be 7.79 and the partition coefficient 2.98.

It has two chiral centres with the *R,R* absolute configuration, which is controlled in the active substance specification by chiral HPLC.

Based on the presented data, neither anamorelin hydrochloride, nor any of its salts have been previously authorised in medicinal products in the European Union. Anamorelin is therefore considered as a new active substance.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance (AS) has been provided in the restricted part of the Active Substance Master File (ASMF) and it was considered satisfactory.

The synthesis of the AS comprises 6 steps using well-defined starting materials with acceptable specifications.

Critical steps and critical process parameters have been identified. Adequate in-process controls are applied during the synthesis. No structurally related impurity was identified as being genotoxic, however two impurities arising from the reagents and solvents were identified as genotoxic - methyl methanesulphonate and 2-chloropropane. The origin and fate of these impurities has been discussed; neither of them has been detected in the active substance. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The synthesis was originally developed by a different manufacturing site. Subsequently the synthesis was transferred to the proposed active substance manufacturer. Slight changes were introduced as a result of transferring the production to the new facility. The active substance used in Phase 1 and Phase 2 clinical studies was provided by the development site, whereas active substance synthesised

using the process of the proposed manufacturer was used for the manufacture of the product used in Phase 3.

Anamorelin HCl is packaged in double low density polyethylene (LDPE) bag with a desiccant unit within and placed in a heat-sealed Mylar/aluminium bag, with final storage in a metal drum (secondary packaging). The polyethylene bags used as primary packaging material are food grade and comply with the requirements of Ph. Eur. and European Directive 10/2011 as amended.

Specification

The active substance specification includes appropriate tests and limits for appearance (visual), identification (IR, HPLC), assay (HPLC), enantiomeric content (PLC), purity (HPLC), water content (KF), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), chloride content (potentiometric), organic impurities (GC) and particle size distribution.

The potential impurities are controlled in the final active substance by validated test methods and the results from three commercial scale anamorelin HCl batches are summarised. As the results are either below detection limit, or not detected, it has been demonstrated that the impurities are generally adequately controlled during manufacturing of the active substance. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from three production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three production scale and three smaller scale batches of anamorelin HCl from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions at 5±3°C and 25 ºC / 60% RH, and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

Samples were tested for appearance, identification, water content, assay, purity, related substances and impurities. The analytical methods and acceptance criteria are the same as applied for release testing and were shown to be stability indicating. No significant changes were observed under either storage conditions or all tested parameters remained within specification.

Photostability testing on one of the smaller scale stability batches following the ICH guideline Q1B was also provided and confirm that the active substance is not sensitive to light. Results on stress testing (heat, basic and acidic conditions, oxidation and hydrogen peroxide degradation) on one of the smaller scale stability batches were also provided. These results confirm that anamorelin HCl active substance was stable under the examined conditions

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of anamorelin HCl stored at controlled temperatures in the proposed container closure system.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as yellow, oval-shaped film coated immediate release tablets, debossed with “HE2” characters on one face, intended for oral administration.

Initially in the clinical development a capsule formulation was used which later evolved to a 50 mg tablet manufactured by dry slugging. The amounts of the excipients were optimised, as were the the extragranular mixture and disintegrant level in order to obtain a dissolution profile similar to that of the 50mg clinical tablet.

The 100 mg film-coated tablet utilised in Phase 3 was based on the 50 mg film-coated tablet used in Phase 2 with minor changes in the manufacturing process, drug load, and excipient levels as described below. Both the 50 mg and 100 mg tablet contain the same inactive ingredients with the exception of the dye utilized in the tablet coating. The 100 mg tablet formulation was originally developed at the manufacturing site which produced the Phase 3 clinical supplies. The formulation and process were then transferred to the proposed site for commercial manufacturing. A comparison of the formulations used in Phase 1, 2, and Phase 3 was presented. The film-coat is merely to improve appearance. The colour of the film coat was changed from blue to yellow during the development as the blue colour faded in photo-stability tests. The level of coat applied has not changed during the development. The tablet shape was changed to oval and debossing introduced.
The dry granulation parameters were optimised and ranges were set following a series of design of experiments (DoEs) at the development site. It has been shown that dry granulation parameters have minimal impact on tablet assay and dissolution. In addition it was shown that granule density is determined by roll pressure, roll speed and screw feed speed. A correlation between granule and ribbon density was identified. Further development steps were conducted during the process transfer to the commercial site. The identified processing ranges were challenged and dry granulation and tablet compression parameters were shown to impact tablet dissolution only at parameters considerably different from the ones established and commercial target settings were confirmed to be well within the studied ranges.

The primary packaging of Adlumiz 100 mg film coated tablets is aluminium /PCTFE blister packs. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process follows the conventional approach for solid dosage forms, employing widely used, non-specialized manufacturing equipment, and comprises the following main steps: pre-granulation blending, dry granulation, post-granulation blending, compression, film coating and packaging. Manufacturing process is considered a standard process and it has been described satisfactorily.

The roller compaction is considered as a critical step in the process; roll pressure, speed and gap of the roller compactor during the dry granulation step are considered critical process parameters.

The in-process controls (IPCs) during the manufacturing process have been presented and are adequately justified. The control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all release specifications.

Holding time for the bulk product is supported based on stability data.

The process will be further validated on three consecutive commercial size batches, according to a provided acceptable protocol.

In conclusion, it is considered that the manufacturing process is sufficiently robust to provide assurance that film-coated tablets of consistent quality, complying with the designated specification, are produced.

Product specification

The finished product release and shelf life specifications reproduced in include appropriate tests and limits for appearance (visual), identification (HPLC, UV), assay of anamorelin HCl (HPLC), impurities (HPLC), dissolution (HPLC), uniformity of dosage units (HPLC, Ph. Eur.), water content (Ph. Eur.) and microbial purity (Ph. Eur.).

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data for 4 commercial and 4 smaller scale batches manufactured by the proposed manufacturer used in as Phase 3 and registration batches manufactured were presented. In addition results from two commercial scale batches by the development site were also presented. All batches are representative of the process and the results show that the finished product meets the proposed specification limits.

Stability of the product

Six batches (three pilot-scale batches and three production-scale batches) of Adlumiz 100 mg film-coated tablets have been studied under long term conditions for up to 36 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guideline. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, assay, impurities, dissolution, water content and microbial enumeration. The methods used were the same as for release testing and are stability indicating. The results of Anamorelin HCl 100 mg film coated tablets stability batches show little change over time and little batch-to-batch variability within specification. No trends were observed.

A photostability study was carried out on one pilot batch of finished product according to ICH Q1B Guideline. The result of the Photostability testing is that Adlumiz film-coated tablets are not affected by exposure to light therefore storage restrictions are not considered necessary.

Forced degradation / stress studies were carried out on one commercial scale batch of finished product in order to demonstrate the stability indicating nature of the assay and related substances methods. Samples of the finished product were tested after exposure photolytic, thermal, acidic, basic, oxidative, and heat/humidity conditions. The results of degradation studies demonstrate that the assay and related substances methods are stability indicating.

Bulk anamorelin HCl tablets are stored in double polyethylene (PE) bags inside a high density polyethylene storage drum with a PE lid with a screw top. Both inner and outer PE bags are cable tied. A silica gel desiccant is placed between the inner and outer bags. Bulk tablets were found stable when stored as described above up to 24 months.

Based on the provided stability data, the proposed shelf life of 36 months stored in the designated commercial packaging material is acceptable.

Adventitious agents

There are no materials of human or animal origin used in the manufacture of the finished product

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development programme for anamorelin HCl consisted of a range of primary pharmacology, safety pharmacology, pharmacokinetic (PK) and toxicology studies, in which pharmacokinetic studies detailed the absorption, distribution, metabolism, and excretion profile of anamorelin HCl, in the toxicity studies anamorelin HCl was given orally (single and repeated dose) and is the same route of administration used clinically.

Toxicity studies were conducted primarily in rats and dogs (up to 26 weeks), including a full battery of genotoxicity, reproductive toxicity studies, local tolerance studies, and a special toxicology study investigating potential effects on tumour growth in nude mice.

Toxicokinetic determinations were conducted in repeated-dose studies up to and including the 28-day rat and the 28-day dog studies. Most of the toxicology studies, and all pivotal studies, were conducted according to Good Laboratory Practice (GLP). No juvenile toxicity studies were completed, as the need for these studies has been waived.

2.3.2. Pharmacology

Ghrelin is the endogenous ligand for the G-protein-coupled ghrelin receptor, which was formerly known as the growth hormone (GH) secretagogue receptor. Previous research into ghrelin and long-acting ghrelin receptor agonists has revealed that ghrelin possesses properties that are anabolic, enhances appetite, increase adiposity, is anti-inflammatory and is pro-kinetic in the gastrointestinal system.

A full battery of safety pharmacology studies has also been completed with anamorelin HCl to review its potential renal, gastrointestinal behavioural and cardiovascular effects.

Primary pharmacodynamic studies

In vitro:

Binding to Ghrelin Receptor:

Anamorelin HCl (Study NN-Hansen B, non-GLP)

The binding affinities of different growth hormone secretagogues (GHS) were examined in an *in vitro* assay using the cloned human ghrelin receptor (GHS-R1a). Binding affinity was determined by competition assay measuring displacement of radiolabeled ibutamorelin (MK-677) following administration of anamorelin. Anamorelin was shown to bind strongly to GHS-R1a with an IC_{50} of 0.69 nM and Ki of 0.37 nM, and this was very similar to that of MK-677 (IC_{50} = 0.67 nM, and Ki = 0.36 nM).

Growth Hormone Release (Study NN-Raun K, non-GLP)

The ability of anamorelin to release growth hormone (GH) was explored using cells isolated from tissue samples obtained from male Sprague-Dawley rats. Anamorelin HCl, Growth Hormone Releasing Hexapeptide (GHRP-6) and MK-677 were tested in concentration ranges from 0.01 nM to 10 pM in at least 3 separately experiments. Dose-response was measured and plotted, with potency (EC_{50}) determined as the concentration inducing half maximal stimulation of the GH release. Anamorelin HCl demonstrated high potency in vitro in comparison to other GHSs with an EC50 of 1.5 nM.

In addition, a number of mature male Beagle dogs were dosed orally once per week with the different GHSs at either 1 mg/kg or 2 mg/kg. Blood samples for pharmacodynamics and exposure were taken 30 min prior to dosing and with frequent intervals 2 to 3 hours post dosing. Dogs dosed with anamorelin HCl displayed significantly high levels of GH release compared to other GHSs (data not shown).

Radioligand Receptor Binding Screen (Study MDS-1016829, non-GLP)

Anamorelin HCl was screened for activity against a battery of over 100 receptors, ion channels, transporters, and enzymes. Anamorelin demonstrated binding to the tachykinin NK_2 site (IC_{50} = 0.021 µM); however, a subsequent NK_2 functional assay demonstrated no functional activity. At the screening concentration of 10 µM, anamorelin demonstrated weak binding to the calcium channel L-type receptors (benzothiazepine and phenylalanine), the serotonin transporter, and the sodium channel.

In vivo:

Growth Hormone Secretion in Rats (Study No. E08QA026, non-GLP)

A single oral dose of anamorelin HCl was administered to male Sprague Dawley rats at a dose of 3, 10, or 30 mg/kg. Blood samples were collected from rats at 0.25, 0.5, 1, 2, 3, 4, 5, and 6 hours after

dosing. GH concentration in plasma sample was measured for each time point and the area under the GH concentration curve (GH AUC_{0-6h}) was calculated from the time course of GH concentration.

Administration of a single oral dose of anamorelin HCl at dosages of 0, 3, 10, or 30 mg/kg, resulted in GH mean peak plasma concentrations of 61, 143, 197, and 251 ng/m, respectively. Mean maximal concentrations at 3, 10 and 30 mg/kg were observed at 2, 2, and 0.5 hours after dosing.

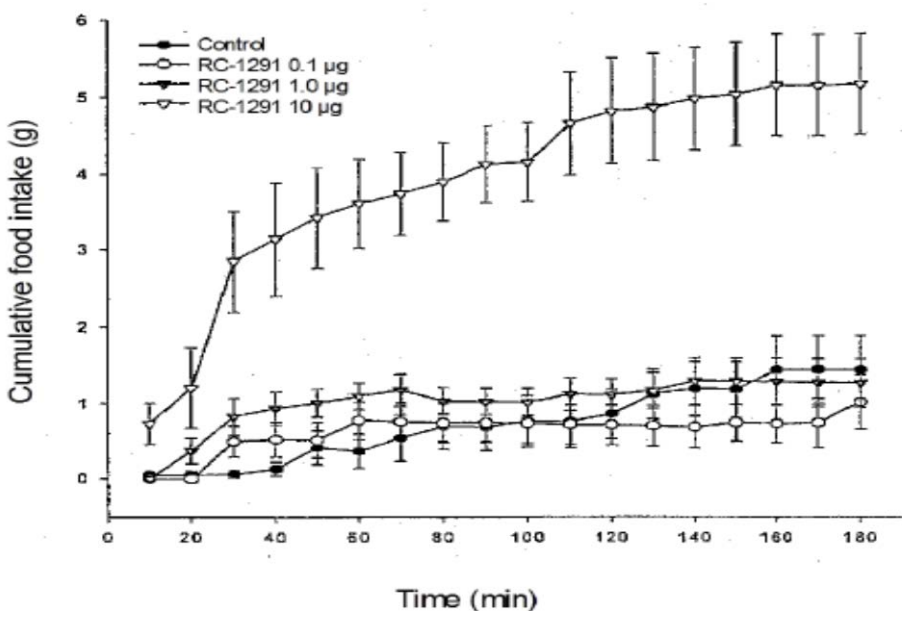
Secondary pharmacodynamic studies

Determination of Orexigenic Effect in Rats (Study No. NN-Brauer MK, non-GLP)

Male Wistar rats were administered 0.1, 1.0 and 10.0 µg RC 26-1291 (anamorelin HCl) via intracerebroventricular (ICV) injection to investigate its orexigenic effect. Food and water intake was monitored with animals allowed free access to lab chow and water.

Anamorelin HCl elicited an increase of food intake with a significant effect seen in the 10 µg dose as can be seen in **Figure 2.**

Figure 2. The effects of increasing doses of RC 26-1291 given ICV to rats on food intake



Growth Hormone and Cortisol Response:

Dogs (Study No NN-Brauer MK & NN-Raun K, non-GLP)

The GH response to single ascending oral doses (0.1, 0.25, 0.5, 1.5 and 3.0 mg/kg) of anamorelin HCl was studied in four fasted male dogs. Plasma was obtained at serial time-points following dosing, and peak growth hormone response (C_{max}) was determined for each dose level as well as for the comparator clinical molecule, tabimorelin. Anamorelin HCl was highly potent and active in dogs following single oral doses (data not shown).

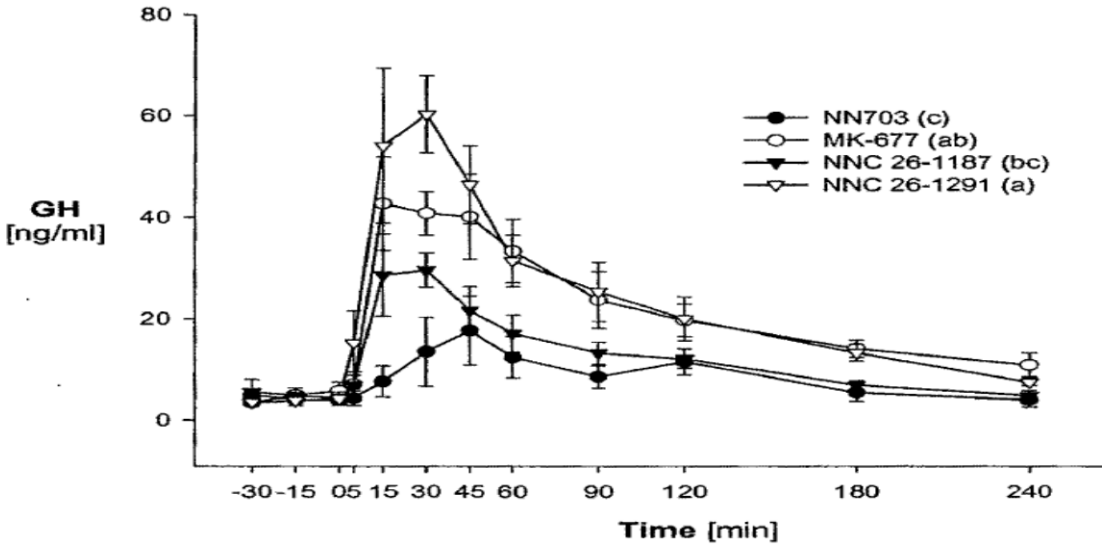
In addition in a study in male fasted Beagle dogs administered a single oral dose of anamorelin HCl (1 and 2 mg/kg), anamorelin-treated dogs demonstrated increased GH levels compared to tabimorelin (data not shown).

Pigs (Study No NN-Brauer MK, non-GLP):

The acute effects of anamorelin HCl and other GHSs on GH and cortisol release were studied following single-dose oral administration of anamorelin HCl to female slaughter pigs. Animals were given 3.5 mg/kg BW/day (5 µmol/kg BW) and blood samples were taken at selected time intervals relative following dosing.

Anamorelin HCl was shown to increase GH (**Figure 3**) and cortisol (data not shown) in pigs, to levels comparable to other GHSs.

Figure 3. Mean growth hormone profile following single-dose oral administration of Anamorelin HCl or other GHSs to female slaughter pigs



Food Consumption and Body Weight Gain (Study No. E08QA018, non-GLP)

This study was performed to examine the stimulatory effects anamorelin HCl on appetite and body weight gain in normal rats. Anamorelin HCl was administered orally to male SD rats once daily for 6 days at doses of 3, 10, and 30 mg/kg. Food intake and body weights were measured daily from the initial day of dosing (Day 1) to Day 7.

Food intake in the anamorelin HCl treated animals was significantly higher than in the control group from Day 2 to 7 at all dose levels. The cumulative change in food intake increased in a dose-dependent manner. Body weight gain in anamorelin HCl-treated rats was significantly higher in all dose groups compared to control animals from Day 2 to 7.

Safety pharmacology programme

Cardiovascular System

In vitro: Cardiovascular - hERG (IKr) Assay (Study No. ZT-REJ-02-01 & ZT-HT-14-01, GLP)

This study was conducted to determine the human ether-à-go-go-related gene (hERG) ion channel blocking profile following the addition of anamorelin HCl in transfected human embryonic kidney (HEK) cells. Anamorelin HCl reduced hERG current in a dose-dependent manner with a concentration of 100 µM producing a 53.2 ± 4.7% reduction in current amplitude. At lower concentrations, anamorelin HCl produced less than a 20% mean inhibition of current amplitude.

This study was repeated with HEK cells chronically exposed (4 hours) to concentrations of 0.1, 1.0, 10 or 100 µM and the hERG IC_{50} was found to be 4.3 µM (Study No. ZT-HT-14-02, see below).

In vitro: Cardiovascular - Langendorff Preparation (Study No. QT-1013, GLP)

To further examinathe functional significance of the sodium and calcium channel binding reported in Study No. MDS-1016829, Langendorff assays were performed using male Hartley guinea pig hearts which were perfused with various concentrations of anamorelin HCl for a minimum of 15 minutes. Bupivacaine, lidocaine, and quinidine were used as positive controls for chronotropy, dromotropy, inotropy and QT liability.

The no effect dose for anamorelin HCl was 10^{-6} M, otherwise anamorelin HCl caused a lengthening of QRS, RR, QT and PQ intervals, and a minor lengthening of ST-T. The changes of QRS prolongation at 1 µM anamorelin was similar to that seen for quinidine at 10^{-5} M and the changes were attributed to partial blockade of Na channels >> K Channels >> Ca channels. The anamorelin concentration that caused prolongation of QRS and decreased dP/dtmax, showed only a very minor liability to affect QTc.

In vitro: Cardiovascular - Effect of Acute Exposure on INa and ICa (L- and T-Type) in Adult Human Cardiac Myocytes (Study No. ZT-HT-14-01, GLP)

This study was conducted to determine the acute effects of anamorelin HCl on the sodium (I_{Na}) and L- and T-type calcium (I_{Ca}) ion currents in acutely isolated adult human atrial myocytes. Blockade of these currents can be associated with QRS and/or PR interval prolongations. Human myocytes were obtained from 6 adult humans and the isolated cells were acutely exposed with anamorelin HCl at concentrations ranging from 0.1 µM to 100 µM. To confirm sensitivity of the cells to blockade of the examined currents, cells were exposed to known selective blockers of either I_{Na}, I_{Ca} (L-type) or I_{Ca} (T-type).

Anamorelin HCl had little effect (less than 20% reduction at 100 µM) on I_{Na} at either a holding potential of -120 mV or a more depolarized potential of -90 mV. A faster pacing rate (1 and 3 Hz) only increased I_{Na} block observed with 100 µM by a mean of 5% or less compared to 0.1 Hz, indicating a lack of rate-dependent block. In addition anamorelin HCl had very little effect on the L-type calcium current (11.6 ± 1.9% reduction at 100 µM) or the T-type calcium current (0.3 ± 5.2% reduction at 100 µM).

In vitro: Cardiovascular - Effect of Chronic Exposure on I_{Na} (Fast and Late) and I_{Ca} (L-Type) in Adult Human Cardiac Myocytes and HEK Cells (Study No. ZT-HT-14-02, non-GLP)

To further explore the mechanism for the modest prolongation of QTc associated with anamorelin, the ion cannel data was used to characterize anamorelin's effect on a cardiac action potential. The mean % decrease obtained from the ion channel data was inputted into an *in silico* model of the human ventricular action potential. This was then used to generate action potential waveforms at 2 basic cycle lengths (BCL) of 1000ms and 500ms. The waveforms were plotted and examined for incidence of arrhythmic events and APD_{20} and APD_{90} were plotted. At no concentration was there evidence of any arrhythmic tendencies (i.e. triangulation or alternans) with anamorelin, even at a free concentration of 100µM. In addition, at a pacing rate of 120 beats/min and over a concentration range spanning 0.1-100µM, there was an equivalent or reduced prolongation of the action potential compared to a pacing rate of 60 beats/min and no arrhythmic signals.

In vivo: Cardiovascular Range-Finder in Dogs (Study No. BM-N104381, non-GLP)

This non-GLP study evaluated the effects of a range of doses of anamorelin HCl on electro-cardiographic (ECG) parameters (rhythm, morphology and interval measurements) in conscious male and female Beagle dogs following oral gavage administration.

A total of eight animals (1M & 1F/group) were dosed with either the vehicle (sterile water for injection) or anamorelin HCl at 5, 6.25, 7.5, 8.75, 10 or 12.5 mg/kg in three Phases. In Phase I, animals received the vehicle or 5, 10, or 12.5 mg/kg in a single dose. In Phase II, the same animals dosed in Phase I received 5, 6.25, 7.5 or 8.75 mg/kg in a single dose. In Phase III, six of the animals dosed in Phases I and II were surgically implanted with intra-cardiac ECG probes and then received 6.25, 7.5 or 8.75 mg/kg in a single dose. Finally, in Phase III-V and III-H, the animals that received the 7.5 mg/kg dose in Phase III received the vehicle and 10 mg/kg of RC-1291.

Changes in cardiac parameters were noted at doses of 10 and 12.5 mg/kg. At 10 mg/kg there was marginal lengthening of QRS duration, and both dogs dosed with 12.5 mg/kg RC-1291 experienced QRS prolongation and extended PQ interval (1st degree AV block). One dog receiving 12.5 mg/kg developed Wenchebach periodicity and high grade 2nd degree AV block.

The no-observed-effect level (NOEL) in this study was 8.75 mg/kg.

In vivo: **Cardiovascular and Pulmonary in Dogs (Study No. BM-N104382, GLP)**

This GLP study evaluated the effects of anamorelin HCl on cardiovascular and pulmonary function in conscious male and female beagle dogs following oral gavage administration. A total of eight animals (4M & 4F) were dosed with either the vehicle or RC-1291 at 0, 1, 5 or 10 mg/kg. Each animal was dosed a total of four times with at least 72 ± 5 hours between doses, and all dogs received each of the doses during the conduct of the study.

Moderate decreases in blood pressure were noted for all anamorelin HCL dose groups for hours 4 through 6 post-dosing. These decreases were statistically significant and of greater magnitude in the male dogs. No compensatory changes in heart rate were observed however.

Evaluation of the ECG intervals revealed PR prolongation and prolonged QRS intervals in high dose group dogs (10 mg/kg) from 0.5 hours post-dosing through 3 hours post-dosing in both sexes (through 6 hours post dosing for PR in males). Maximum PR prolongations were observed in both sexes at 1.25 hours post-dosing with nominal increases of 27 msec for the males and 31 msec for the females. The QRS changes in the 10 mg/kg group were nominally 19 msec for the males and 18 msec for the females when compared to vehicle. At the mid-dose level (5 mg/kg), moderate to slight prolongations were observed, and only the changes noted at 10 mg/kg were considered to be clinically significant. No prolongation of QT was observed at any of the dose levels.

There were no test article-related alterations associated with the pulmonary parameters (respiratory rate, tidal volume and minute volume).

In vivo: Intravenous Cardiovascular in Dogs (Study No. BM-05103, GLP)

The purpose of this study was to determine the effects of anamorelin HCl on conscious telemetered male and female Beagle dogs after a 30-minute IV infusion and to further explore the causes of prolongation of PR intervals and QRS durations, and decreases in blood pressure seen in previous oral cardiac safety studies in dogs. Five male and five female dogs were each administered escalating 30-minute infusions of eight dose levels of anamorelin HCl.

The most significant finding in this study was a moderate to marked decrease in blood pressure noted in all animals, at all dose levels, that was treatment but not dose-related. There was no NOEL for effects on blood pressure. No other adverse clinical signs noted in any animal administered up to 1 mg/kg.

In terms of cardiac changes, both PR and QRS periods were prolonged in a dose-dependent manner. Changes were noted from 1 mg/kg in females, and from 2 mg/kg in males, although at these lower

doses were not considered great enough to affect the health of the animals. Significant changes were detected at 4 mg/kg, in which PR intervals prolonged for 30.6 msec and 36.3 msec; and QRS duration prolonged for 6.2 msec and 5.9 msec; for males and females, respectively. Both PR and QRS periods remained elevated compared to control animals post-dose, for between 2.2 and 3 hours (QRS duration), and for up to 12 hours (PR interval). One male administered 3.5 mg/kg had a peak prolongation in QRS duration of 11.4 msec and two males and one female administered the 4 mg/kg dose level had prolongations in QRS durations of 9.3, 10.1 and 9.2 msec, respectively. The No-Observed-Adverse-Effect-Level (NOAEL) for ECG changes in this study was considered to be greater than 4 mg/kg. Mean C_{max} at 4 mg/kg in males and females was 3072 ng/mL.

Central Nervous System (CNS)

Modified Irwin Screen (FOB) in Rats (Study No. IR-21866, GLP)

The ability of anamorelin HCl to effect general behaviour in rats was explored in a Modified Irwin Screen Test in male SD rats. No treatment-related changes in behaviour, locomotor activity, tremor or pain response were observed in any of the anamorelin treated dose groups.

Locomotor Activity in Rats (Study No. IR-21990, GLP)

Anamorelin HCl was administered orally by gavage to 3 groups of 5 male rats at 10, 25 or 50 mg/kg. No changes were noted for anamorelin HCl-treated rats at any dose.

Body Temperature in Rats (Study No. F07PD003, GLP)

The influence of anamorelin HCl on the body temperature was assessed in male SD rats aged 6 weeks, administered orally with a single doses ranging from 10 to 100 mg/kg.

The only significant finding was of body temperature showing a decrease (maximum: 1.98°C) in the 100 mg/kg group at 2 and 4 h after administration. No other changes were noted and so the NOEL was 50 mg/kg.

Gastrointestinal

Intestinal Motility (Charcoal Propulsion) in Rats (Study No. IR-21824, GLP)

To investigate the effect on gastrointestinal motility, anamorelin HCl, atropine and vehicle were administered orally to male SD rats. Treatment with the positive control, atropine resulted in reduced charcoal motility (53.2%). A similar but lesser effect (66.8%) was noted in the highest dose of anamorelin HCl treated group (50 mg/kg). The NOEL for gastrointestinal motility was 25 mg/kg.

Renal

Renal Function in Rats (Study No. IR-22444, GLP)

Anamorelin HCl had no significant effect on renal function in male SD rats given 10, 25 or 50 mg/kg.

Pharmacodynamic drug interactions

No studies were submitted.

2.3.3. Pharmacokinetics

The applicant submitted a full range of studies to examine the absorption, distribution, metabolism and excretion of anamorelin HCl in in vitro and in vivo test systems. In addition an in vitro program to explore potential drug-drug interactions (DDI) has been undertaken with anamorelin HCl.

Absorption

Absorption data were obtained from studies conducted in rats, pregnant rabbits and dogs with anamorelin HCl administered either orally by gavage (up to 28 days) or intravenously (**Table 1**).

Table 1. Tabulated summary of non-clinical absorption data with anamorelin HCl

Study ID	**Type of Study**	**Species N/Gender**	**Route, Dose**	**Results**
IR22438	Single dose BV of free base	**Rats** 5M, 5F	Oral 50 mg/kg BW IV 0,6 mg/kg BW	Oral availability is 50 (M) and 56%(F), $T_{1/2}$ 1.27-2.17 h, T_{max} 0.5 hr post dose C_{max} following oral dose is 759 (M) and 1021 ng/mL (F) Bi-exponential decline in plasma-concentration (IV)
IR-22439	Single dose BV of free base	**Dogs** 2M, 2F	Oral 1 mg/kg BW IV 0,05 mg/kg BW	Much lower plasma concentrations in males: BV was 8 (M) and 57% in F T_{max} 1.25-2 h post dose $T_{1/2}$ 0.75-1.3 h
IR-22491	Single dose BV	**Dogs** 1M, 1F	IV 0,05 mg/kg BW	Bi-exponential decline in plasma-concentration No gender effect $T_{1/2}$: 1.12 (M)-1.23 (F) hr AUC $_{0-t}$ (ng h/ml): 17.1 (M) 22 (F) C_{max} 24 (M), 27.6 (F) ng/ml
IR-22140	BV 7 days	**Dogs** 1M, 1F	Oral 5 mg/kg BW	BV 74 (M) and 100(F) % (IV data from IR-22491) T_{max} 0.25 h post dose day 1 T_{max} 0.75 h post dose day 7 $T_{1/2}$: 0.757 (M)-1.98 (F) hr Cmax and AUC were approximately 2-fold higher in F than the M No sign of accumulation
IR-22861 GLP-compliant	PK Up to 19 days	**Dogs** 4M, 4F	Day 1:SD 0.25 mg/kg BW IV	Increased BV with increased oral dose Slightly higher oral BV in F Non-linear single dose PK

			Days 5,9,15,19: 0.1; 0.5; 1.0; 5 mg/kg BW oral	

Distribution

Radiolabelled [14C]-anamorelin HCl tissue distribution was investigated in Sprague Dawley albino rats and melanin binding as well as mass balance were investigated in Sprague Dawley albino rats and pigmented Long Evans rats, administered a single oral dose of 30 mg/kg labeled C14-anamorelin HCl for comparison (Study QI-PK04-043; non-GLP).

There was no relevant difference in binding of radioactivity between pigmented Long Evans and non-pigmented albino Sprague Dawley rats, suggesting no binding of anamorelin to melanin (data not shown)

Following oral administration, there was negligible (<0.3%) accumulation of radioactivity at any time point in any tissue outside of the gastrointestinal tract. Within the gastrointestinal tract, the greatest concentrations of radioactivity were 10.09% and 2.70% in the luminal (small intestine) and non-luminal (liver) tissues, respectively. Concentrations of radioactivity in the gastrointestinal tract tissues declined promptly such that all tissue concentrations were <1.0% of the administered dose from 24 h post-dose and later.

The longest apparent terminal elimination half-lives occurred in brain (655.7 h), eyes of Long Evans rats (424.7 h), heart (424.2 h), and plasma of Long Evans rats (354.9 h). However, the mass of radioactivity upon which these estimates were based was in each case _0.051% of the administered dose.

Plasma protein binding

^{3}H-anamorelin bound relatively high to the plasma proteins of male and female rat, dog and human volunteers over the concentrations investigated (0,1; 0,3; 1 µM). The extent of plasma protein binding was independent of concentration or gender. Plasma protein binding varied between species and was ranked; rat (92-94%) < dog (96-97%) < human (97-98%) (Study IR-22835).

Blood Plasma Ratio

Assessment for potential preferential binding of anamorelin to whole blood or to plasma was investigated in dogs administered either an oral dose of 1 mg/kg or an intravenous dose of 0.25 mg/kg [3H]-anamorelin. Whole blood to plasma ratios were less than 1 for all samples indicating that [3H]-anamorelin did not preferentially associate with red blood cells (as part of Study IR-23002, excretion).

Metabolism

Metabolism of anamorelin HCl has been investigated using *in vitro* studies with hepatic microsomes prepared from humans, rats and dogs, and with cytochrome P450 isoforms (CYP isoforms). Two studies were conducted to determine metabolism of anamorelin HCl in hepatic microsomes extracted from rats, dogs and humans.

In the first study (Study IR-22588), following 45 minute incubation with 15 µM [^{3}H]-anamorelin, seven anamorelin metabolites were identified in all three species and these metabolites. The main metabolites in rat microsomes were metabolites 1, 2, 3 and 5, each accounting for from 5.31% to 16.25% of total radioactivity. In dogs and humans the same metabolites were formed, of which the

most abundant were M2 and M5, accounting for 3.88% (M2, human) and 5.70% (M2, dog), 2.92% (M5, human) and 7.32% (M5 dog) of total radioactivity. From this study it can be concluded that all human metabolites were also formed in animal species (rat and dog), and that there were no human specific metabolites.

In the second study (Study AMRI-BD000039), following a four hour incubation of RC-1291 (anamorelin HCl) with both hepatic microsomes and recombinant CYPs, ten metabolites of anamorelin were detected, of which the main metabolites were M4 and M6.

In addition to M4 and M6, a number of other anamorelin metabolites have been detected on completion of clinical study. These are listed as the four main metabolites (M3, M4, M6, and M11) detected in faeces and one conjugated metabolite (M12) detected in urine. Each of these metabolites contributed to less than 10% of the administered radioactive dose and these are not considered to be major human metabolites (Study AMRI BD000054 and Clinical Study RC-1291-103).

Anamorelin undergoes hepatic metabolism, and is primarily metabolised by CYP3A4 (>99%), with very minor contribution from CYP2C8 (0.27%) and CYP2D6 (0.05%). Metabolism occurs by a combination of cytochrome mediated oxygenation and N-demethylation metabolic pathways leading the formation of these 12 metabolites.

Excretion

Excretion was studied in rats and dogs using single dose, radiolabelled [3H]-Anamorelin HCl given orally and by IV-infusion (main GLP-compliant studies IR-23001 and IR-23002). In rats have almost all of orally administered anamorelin HCl was excreted in faeces, and only a small proportion was excreted as urine (1.5%) or as expired air (0.02-0.03%). In dogs this pattern was replicated although only 74.7% of orally administered dose was excreted in faeces and 11% was excreted as urine. In both species the majority of the administered dose was eliminated within the first 24 hours.

Pharmacokinetic drug interactions

The potential of anamorelin HCl to inhibit human CYP450 isozymes was investigated (Studies No. IR-22377, GLP, . CR-196103, non-GLP, performed in a GLP lab, CR-31033, GLP) and no significant findings of inhibition were found with CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2B6 and CYP2C8. Inhibition of CYP3A4 was observed, an IC_{50} of 11.34 µM was estimated although it is noted that this level is in excess to anticipated clinical exposure following dosing with 100 mg in humans, the potential interaction of anamorelin with other strong CYP3A4 inhibitors or inducers is entirely possible.

The ability of anamorelin HCl to induce CYP isoenzymes was also evaluated in human hepatocytes (Study CR-196632, non-GLP, performed in GLP lab) and it was determined that anamorelin HCl did not significantly induce CYP3A4, CYP2B6 or CYP1A2.

A comprehensive battery of *in vitro* transporter assays was conducted to provide data on the interaction of anamorelin HCl with the human efflux transporters and the human uptake transporters. Anamorelin HCl was found to inhibit P-gp mediated transport of [3H]-digoxin by 46.2% at a high concentration (120 µM) in an *in vitro* study (Study Y09AG025, non-GLP).

The potential interaction of anamorelin HCl with other drug transporters were investigated in Study SB-Helsinn-05-04 (non-GLP).

Anamorelin HCl was shown to be a weak inhibitor of the human ABC transporters: BSEP (ABCB11/sP-gp), MRP2 (ABCC2), and BCRP (ABCG2/MXR) with IC50s of more than 200 µM.

Anamorelin did not inhibit OATP1B1 or OAT3 at concentrations of up to 300 µM and showed a weak to moderate inhibition activity of MATE1, MATE2-K, OATP1B3, OAT1, OCT1 and OCT2 ranging between 7.7 to 218 µM.

Additionally, this *in vitro* study showed that anamorelin is a substrate for MDR1 and OATP1B3 with low passive permeability, as indicated by Papp values observed in this study ranging from approximately 1 to approximately 8 x 10-6 cm/s at 100 µM, where active transport is saturated or in the presence of PSC833 (10 µM), an inhibitor of MDR1.

2.3.4. Toxicology

The toxicological programme for anamorelin HCl has been completed in oral toxicity studies with mice, rats, rabbits and dogs. General toxicity was administered to rats and dogs for periods of up to 6 months. A full battery of genotoxicity and studies in reproductive and development toxicity consisted of fertility/early development and embryofetal development. Carcinogenicity, pre/post-natal and juvenile toxicity studies were not submitted. Local tolerance and a mouse xenograft studies have also been completed.

Single dose toxicity

A summary of the single dose toxicity studies is provided in **Table 2**.

Table 2. Summary of completed single dose toxicity studies with anamorelin HCl

Study ID	**Species/ Sex/Number/ Group**	**Dose (mg/kg)/Route**	**Approx. lethal dose / observed max non-lethal dose (mg/kg)**	**Major findings**
IR-21868 GLP	Mice CD-1 Prelim: 2F/Group Main: 5M & 5F/Group	Prelim: 0, 200, 400 and 1000 mg/kg Main: 400 and 600 mg/kg Oral	LD_{50}≥400 NLD=200 NOEL=ND	2M & 2F died at 400 mg/kg. All animals died at 600 mg/kg. Subdued behaviour at 200 mg/kg Due to findings of subdued behaviour, no NOEL was determined.
IR-21918 GLP	Mice CD-1 2F/Group	2, 10, 15 and 20 mg/kg IV	LD_{50}=20 NLD=15 NOEL=ND	Mortality at 20 mg/kg Subdued behaviour at 15 mg/kg Dark tails at ≥ 2 mg/kg

IR-21988 GLP	Rats Sprague Dawley Prelim: 2F/Group Main: 5M & 5F/Group	Prelim: 100 and 200 mg/kg Main: 100 and 200 mg/kg Oral	LD_{50}=200 NLD=100 NOEL=ND	Mortality at 200 mg/kg 100 mg/kg: Laboured breathing, ↓BW gain. Due to findings of laboured breathing, no NOEL was determined
IR-21867 GLP	Rats Sprague Dawley Prelim: 2F/Group Main: 5M & 5F/Group	Prelim: 0, 2, 10, 15 and 20 mg/kg Main: 10mg/kg IV	LD_{50}=10 NLD=2 NOEL=2	Mortality at ≥ 10 mg/kg Laboured breathing, staggering and subdued behaviour at 10 mg/kg. Intravenous NOEL at 2 mg/kg

NLD=non-lethal dose; LD_{50}=median lethal dose; NOEL=no-observed effect level; F=female; M=male; ↓=decrease; BW=body weight

Repeat dose toxicity

A summary of the repeat dose toxicity studies is provided in **Table 3**.

Table 3. Summary of completed single dose toxicity studies with anamorelin HCl

Study ID	**Species/ Sex/Number/ Group**	**Dose (mg/kgBW/day)/ Route**	**Duration**	**NOEL/ NOAEL (mg/kg BW /day)**	**Major findings**
IR-21710 Non-GLP	Rats Sprague Dawley 5M + 5F	0, 25, 50, 100, 150 oral 1/10 IV	7 days Single dose	0/25 1	Irregular respiration piloerection F only: body weight gain at all dose levels 1F dead after 10 mg/kg IV No clinical signs after 1 mg/kg IV
IR-22727 GLP	Rats Sprague Dawley 10 M + 10 F Further 5M + 5F for TK	0, 15, 30, 60 oral	28 days With TK	0/15	Subdued behavior, irregular respiration and nasopharyngitis at 30 mg/kg Mortality at 60 mg/kg Moderate weight gain in Females Inflammation of the upper GI tract at all dose levels by local irritation

MPI-1109-001 GLP	Rats Sprague Dawley 25 M + 25 F	0, 5, 30, 45 oral	13 weeks + 6 weeks recovery Without TK	0/45	10% increase in body weights in both genders (reversible) 2M + 5F died as a result of dosing error No other findings
MPI-1109-003 GLP	Rats Sprague Dawley 15 M + 15 F	0, 15, 30, 45 oral	26 weeks without recovery without TK	0/30	Up to 10% body weights gain in both genders and all treatment groups 5 F at 45 mg/kg/day showed minimal to moderate increases in AST, ALT and SDH No pathological changes related to treatment No other findings

IR-21857 Non-GLP	Dogs: beagle Part A/1: 1M + 1F Part A/2: 1M + 1F Part B: 1M + 1F	Oral range finding Part A/1: 2.5; 5; 15 Part A/2 5; 10 Part B: 5	 3 days 14 days 14 days	 5/5 5/5 5	1F: Mortality due to cardiotoxicity at 15mg/kg 2hours after the first dose Heart weight increase 1M: after the third dose 15mg/kg had severe arrhythmia and QRS complex prolongation Emesis; animal killed At 10 mg.kg-1.day-1, very minor prolongation of the QRS complex in the M was observed, but within normal limits. There was no difference in the daily variation in the ECGs in the same animal during the treatment period at 10 mg.kg-1.day-1. No other findings Plasma concentration at 1 h post dose for Part A/2 : max. after 10 mg/kg on day 22: 2570 ng/ml (M) 3270 ng/ml (F) No findings
IR-22728 GLP	Dogs: beagle 4M + 4F	Oral gavage 0, 1, 3, 5	28 days with TK	1 /3	F: at 5 mg/kg slight elevation in ALT, mild to moderate periportal inflammation in the liver, increased pigmentation in Kupffer cells and some hepatocytes No other findings

MPI-1109-002 GLP	Dogs: beagle 7M + 7F (3 out of these 7 for recovery)	Oral 0, 1, 3, 5	13 weeks with 6 weeks recovery without TK	0/3	5-10 % body weight gain in all treatment groups, reversible; No treatment-related ECG-changes 1M: at 5mg/kg elevated ALP, AST, SDH Mild bile duct hyperplasia with inflammation and fibrosis in the liver Moderate glandular cystic hyperplasia of the gallbladder which was not reversible
MPI-1109-004 GLP	Dogs: Beagle 4M + 4 F	Oral 0, 1, 3, 5	26 weeks without recovery without TK	0/0	5-10 % body weight gain in all treatment groups, not dose-related No treatment-related ECG-changes Sporadic minor increases in some clinical chemistry parameters, e.g. ALP, ALT, AST, SDH not dose-related No other treatment-related findings Control and all treatment groups: minimal degrees of: cortical tubular degeneration, inflammation of the liver atrophy of the thymus gland, tubular mineralization of the kidneys

Genotoxicity

Table 4. Genotoxicity studies performed with anamorelin

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria / IR-21717 / yes	Salmonella strains TA98,100, 1535, 1537, E. coli WP2uvrA	+/- S9, 0, 31, 63, 125, 250, 500, 1000 µg/plate	no increase in revertants, bacteriotoxicity ≥ 500 µg/plate
Chromosomal aberrations in	CHO-cells	Test 1: 6 h treatment, +/-	no increase in structural or numerical aberrations at 6 h and

mammalian cells / IR-22017 / yes		S9: 0, 39, 78, 156 µg/ml Test 2: 6 h treatment, + S9: 0, 75, 100, 150 µg/ml Test 2: 6 h treatment, - S9: 0, 40, 75, 100 µg/ml Test 2: 22 h treatment with 24h and 48 h harvest, - S9: 0, 20, 40, 75 µg/ml	22 h treatment with 24h harvest increase in polyploidy and endoreduplication at 48 h harvest cytotoxicity observed at 6 h treatment +/–S9 ≥ 156 µg/ml and at 22 h treatment + S9 ≥ 150 µg/ml and at 22 h treatment – S9 ≥ 75 µg/ml
Chromosomal aberrations in vivo / IR-22285 / yes	Mouse CD-1, micronuclei in bone marrow	0, 50, 100, 200 mg/kg/d, oral gavage group size: vehicle contr: 5 M and 5 F 50, 100 mg/kg: 5 M 200 mg/kg: 10 M, 10 F pos contr: 5 M	no increase in micronuclei in bone marrow erythroblasts clinical signs: 1 dead in 200 mg/kg dose group, clinical adverse effect signs: hunched posture, subdued behavior

Carcinogenicity

No studies were submitted.

Reproduction Toxicity

The reproductive and developmental toxicity of anamorelin HCl was evaluated in a fertility and early embryonic development study in rats and embryo-fetal development studies in rats and rabbits.

Table 5. Summary of fertility/ early-embryo-fetal development toxicity study in rats

Study type/ Study ID / GLP	Species; Number group	Route & dose(mg/kg/day)	Dosing period	Major findings	NOAEL (mg/kg/day)
Study No.: 8002-107 Fertility and embryo-fetal development study GLP	Sprague Dawley Rat (Crl:CD(SD)) 22/sex/group	0, 15, 30, 60 oral	Males: 28 days prior to mating until necropsy Females: 14 days prior to mating and up to day 7 of gestation	Control: 1 death 15 mg/kg/d: 1 death ≥ 30 mg/kg**:** 2 deaths, ↑body weight gain, ↑ body weight, ↑ food consumption	NOAEL reproductive parameters: 60 NOAEL female fertility, early embryonic development: 60

Table 6. Oral Developmental Toxicity Study in Rats and Rabbits (Pivotal Studies)

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose(mg/ kg/day)	Dosing period	Major findings	NOAEL (mg/kg/day)
Study: CL-7591-100 dose range finding embryo-fetal development study	Sprague Dawley Rat (Crl:CD(SD) 6/group	0, 15, 30, 45, 60,80, 100, 125 oral	Gestation day 6 through 17	≥80 mg/kg/d: audible/labored respiration, ↓ body weight, ↓ gravid uterine weight ↓ fetal body weight (slightly) 100 mg/kg/d: 2 deaths 125 mg/kg/d: 1 death	
Study: CL-8002-105 embryo-fetal development study and toxicokinetics GLP Study	Sprague Dawley Rat (Crl:CD(SD) 25/group	0, 15, 30, 80 oral	Gestation day 6 through 17	**Maternal:** All treated groups: ↑body weight gain, ≥75 mg/kg/d: ↑ body weight, ↑ food consumption 80 mg/kg/d: audible/labored respiration ↓ body weight gain	maternal toxicity NOAEL: 30 NOAEL embryo fetal development: 80
Study: CL-8002-106 dose range finding embryo-fetal development study and toxicokinetics	Rabbit/ Hra:(NZW)SPF 6/group	0, 25, 50, 75, 100 0, 75, 100,125, 150	Non-pregnant phase: 5 days before Pregnant phase: GD 7 to 20	All doses: recumbency, post dose hypoactivity ≥75 mg/kg/d: squinted eye, few or no feces, cyanotic appearance, tremors, irregular, respiration, ↓ food consumption, ↓ body weight, ↓ body weight gain ≥100 mg/kg/d mortality, ↓ mean gravid uterine weight	
Study: CL-8002-106 embryo-fetal development study and	Rabbit/ Hra:(NZW)SPF 20/group 3/group	0, 10, 30, 75/50[1] oral/SC	Gestation day 7 through 20	**Maternal:** 75 mg/kg/d: 5 deaths ≥75 mg/kg/d: ↑ hypoactivity,	maternal toxicity NOAEL: 30

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose(mg/ kg/day)	Dosing period	Major findings	NOAEL (mg/kg/day)
toxicokinetics GLP	toxicokinetics			tremors ataxia, rapid respiration	NOAEL fetal development: 50

[1] Due to the number of early deaths, the high-dose concentration was decreased from 75 to 50 mg/ml.

Toxicokinetic data

The applicant resented tables of mean (male and female) Cmax and AUC toxicokinetic data obtained from the general toxicity and reproductive toxicity studies. The TK data below are for measurements taken following first dose administration.

Table 7. Comparison of Anamorelin Cmax Data across Species for Single Dose Administration

Dose	Human Equivalent Dose (HED)		Mean C_{max} (ng/mL) *				
			Rat	Dog	Pregnant Rat	Pregnant Rabbit	Human
	(mg/kg)	(mg/m^2)	Male and Female	Male and Female	Female	Female	Male and Female
100 mg	1.5	55.5	–	–	–	–	738
150 mg	2	74.4	–	–	–	–	1281
200 mg	2.5	91.4	–	–	–	–	1223
300 mg	4	146	–	–	–	–	1977
400 mg	4.8	177	–	–	–	–	3493
1 mg/kg	0.556	20	–	162	–	–	–
3 mg/kg	1.67	60	–	748	–	–	–
4 mg/kg	2.22	80	–	3072	–	–	–
5 mg/kg	2.78	100	–	2030	–	–	–
15 mg/kg	2.42	90	81.9	–	–	–	–
30 mg/kg	4.84	180	555	–	–	–	–
45 mg/kg	7.26	270	–	–	–	–	–
60 mg/kg	9.68	360	992	–	–	–	–
80 mg/kg	12.9	480	–	–	1190	–	–
75 mg/kg	24.2	900	–	–	–	2129	–

Table 8. Comparison of Anamorelin AUC Data across Species for Single Dose Administration

Dose	Human Equivalent Dose (HED)		Mean AUC (ng*hr/mL) [a]				
			Rat	Dog	Pregnant Rat	Pregnant Rabbit	Human
	(mg/kg)	(mg/m^2)	Male and Female	Male and Female	Female	Female	Male and Female
100 mg	1.5	55.5	–	–	–	–	2126
150 mg	2	74.4	–	–	–	–	2965
200 mg	2.5	91.4	–	–	–	–	3071
300 mg	4	146	–	–	–	–	5782
400 mg	4.8	177	–	–	–	–	8992
1 mg/kg	0.556	20	–	248	–	–	–
3 mg/kg	1.67	60	–	1052	–	–	–
4 mg/kg	2.22	80	–	3076	–	–	–
5 mg/kg	2.78	100	–	3020	–	–	–
15 mg/kg	2.42	90	236	–	–	–	–
30 mg/kg	4.84	180	1378	–	–	–	–
45 mg/kg	7.26	270	–	–	–	–	–
60 mg/kg	9.68	360	3878	–	–	–	–
80 mg/kg	12.9	480	–	–	5380	–	–
75 mg/kg	24.2	900	–	–	–	8993	–

Local Tolerance

Local tolerance studies were conducted to determine potential irritating effects of anamorelin HCl on the skin and the eyes. In a primary skin irritation assay conducted in rabbits, anamorelin HCl was determined to be a nonirritant (Study CR-UFF00001). An *in vitro* assay conducted on isolated bovine corneas showed anamorelin HCl had scores indicative of a moderate eye irritant compared to the positive control, imidazole, a sever eye irritant (Study IIVS-05AG37.350069).

Other toxicity studies

The potential effect of anamorelin HCl on tumor growth was assessed in a lung cancer mouse xenograph model. In this study, nude mice transplanted with an A549 human NSCLC adenocarcinoma tumor cell line and administered up to 30 mg/kg/day anamorelin HCl or 2 mg/kg/day of ghrelin for 28 consecutive days showed moderate increases in body weight, growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels, and no effect on tumor growth (Study PR-A549-e312-e313-e50-RJV-01).

2.3.5. Ecotoxicity / environmental risk assessment

Table 9. Summary of main study results

Substance (INN / Invented Name): Anamorelin HCl			
CAS-number (if available): 861998-00-7 (salt), 249921-19-5 (free base)			
PBT screening		Result	**Conclusion**

Bioaccumulation potential- log K_{ow}	Potentiometric method	Log Kow = 2.98	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (prevalence by literature)	0.0081	µg/L	> 0.01 threshold (N)

2.3.6. Discussion on non-clinical aspects

The non-clinical development programme for anamorelin HCl consisted of a range of primary pharmacology, safety pharmacology, pharmacokinetic and toxicology studies.

In all animal studies conducted the systemic exposure of the test animals was in the range of or only slightly above the clinical exposure. The lack of appropriate safety margins throughout the non-clincial programme was noted by the CHMP, as it did not offer any assurance that findings from these studies would not also apply in the clinical setting

Anamorelin HCl displays high affinity binding to the ghrelin receptor, and weak inhibitory activity at sodium and calcium channels. *In vivo* studies completed with anamorelin HCl demonstrated that there was robust GH release following oral administration to rats, pigs and dogs. Increases in body weight and food intake were also observed in treated male rats.

The applicant did not investigate any pharmacodynamic interactions and this was considered acceptable on the basis of the short acting nature of anamorelin together with the lack of evidence of interactions with chemotherapeutic agents utilized in the clinical development. The Phase 2 and 3 clinical trials were designed in patients with lung tumors taking mainly paclitaxel, carboplatin and bevacizumab. In literature there are no described specific interactions between these compounds and GH or GH-release compounds such as anamorelin.

A safety pharmacology programme was completed and anamorelin HCl had no clinically relevant effects on general behaviour, locomotor activity, pulmonary function, intestinal motility, or renal function. Due to concerns for potential cardiotoxicity a comprehensive cardiovascular safety programme in vitro and in vivo was completed.

The *in vitro* study in HEK cells suggests a weak hERG blocking activity for anamorelin HCl.

The hERG IC50 was found to be 4.3 µM, although significant blockade is unlikely to transpire clinically since this is more than a 100-fold higher than the free plasma concentration of anamorelin HCl (~40 nM). *In silico* modelling has shown that anamorelin HCl was not pro-arrhythmic, despite prolonging action potential duration. In humans prolongations in QRS and PR intervals were observed in subjects treated with 300 and 400 mg anamorelin HCl. As a result of safety pharmacology studies it was concluded that anamorelin has the potential to increase a cardiovascular risk in humans.

Ventricular arrhythmias due to PR/QRS prolongation are proposed as an important potential risk for anamorelin HCl in the applicant's RMP.

Studies to examine the absorption, distribution, metabolism and excretion of anamorelin HCl in *in vitro* and *in vivo* test systems were provided. In addition an *in vitro* program to explore potential drug-drug

interactions (DDI) was undertaken with anamorelin HCl. Absorption of anamorelin HCl is rapid, although oral bioavailability ranged from 6-18% in rats to 74-100% in dogs. Distribution was limited to the gastrointestinal tract and liver, with some very limited distribution to brain, eyes and the heart. There are no data in bile-conducted animals. Considering the lack of accumulation, data in bile duct cannulated animals can be omitted. Enterohepatic recycling as a cause of the double peaks in anamorelin plasma concentration-time profiles can be ruled out. Anamorelin HCl is highly bound to plasma proteins (92-98%). Metabolism is primarily hepatic (CYP3A4) via oxygenation and N-demethylation metabolic pathways leading the formation of 12 metabolites (M1-12). Each of these metabolites are identified as being minor, and two unique human metabolites (M11 and M12) are only present in excreta, so are not present in human plasma.

There was no relevant difference in binding of radioactivity between pigmented Long Evans and non-pigmented albino Sprague Dawley rats, suggesting no binding of anamorelin to melanin. No formal phototoxicity assessment and testing according to ICH S10 was performed. It was agreed that in light of the negative binding to melanin and the extensive re-evaluation of clinical data with a focus on phototoxicity in treated patients this approach was acceptable.

Potential interactions at P-gp between anamorelin and P-gp inhibitors in the GI-tract and the impact on the tolerability of anamorelin have to be considered in terms of clinical relevance. As a consequence, the applicant proposed to include interactions with P-gp substrates as an important potential risk in the Risk Management Plan.

Toxicity studies were conducted primarily in rats and dogs (up to 26 weeks), including a full battery of genotoxicity, reproductive toxicity studies, local tolerance studies, and a special toxicology study investigating potential effects on tumour growth in nude mice. Toxicity findings were primarily for nasopharynx irritation in rats, cardiotoxicity in dogs and mild to moderate signs of changes to liver transaminases in both rats and dogs.

The observed cardiotoxicity findings were reflected in the proposed SmPC, which stated that in dogs anamorelin induced prolongation of both the QRS and the PQ interval (the latter leading to AV-block) at oral doses of > 10 mg/kg.

Even though, the hepatic changes were mild and/or sporadic, a relationship to anamorelin HCl treatment was considered likely. Furthermore, significant hepatic changes were also observed in the clinical programme. Such that its use in hepatic-impaired subjects must be further explored, especially due to its metabolism profile. As a result, use in hepatic-impaired subjects must be further explored especially due to its metabolism profile, and the applianct included use in hepatic impaired subjects as missing information in the RMP.

In terms of toxicokinetics, measurements were taken only in the completed 28 day studies due to an assumption of linear kinetics across both rat and dog species. Safety margins are thus extrapolated from no adverse effect levels identified in the long-term toxicity studies.

Anamorelin HCl was not genotoxic when tested in both *in vitro* and *in vivo* assays. The need for carcinogenicity studies has been discussed on the basis of the life-expectancy of the treatment population, in line with the ICH S1A Guideline. The effects of anamorelin on tumour growth were evaluated in a mouse xenograft model. Treatment of anamorelin HCl for 28 days had no effect on tumour growth, while it increased plasma GH levels and increased changes in body weight. The findings of this study confirm published data that an increase in tumour formation is unlikely as a result from increased GH and IGF-1 levels. However, no long-term data are available and therefore no definitive conclusion on the influence of anamorelin on tumour growth can be drawn. Tumour progression was also included in the RMP as an important potential risk.

No significant effects on fertility and reproductive toxicity were determined in studies in rats and rabbits however margins for safety are low. The applicant has not provided any studies to describe pre- and post-natal effects given the indication for Adlumiz, however the proposed sections of 4.6 and 5.3 of the SmPC reflect these inadequacies in the reproductive toxicity studies.

Based on the ERA study results submitted anamorelin is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Anamorelin has been characterised in non-clinical pharmacology, pharmacokinetic and toxicology studies. Of particular concern were the observed signals of cardiotoxicity and hepatic changes, especially in light of the exposure levels used in the non-clinical studies, which were only slightly above the expected clinical exposure in humans. These issues are further discussed in subsequent sections of this report. Other signals arising from non-clinical studies including ventricular arrhythmias, tumour progression and interactions with P-gp substrates were proposed as important potential risks in the RMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

A triggered GCP inspection at two clinical investigator sites and one CRO site was requested by the CHMP, to verify GCP compliance, in particular on the handling, processing and reporting of safety data and also on the verification of selected efficacy and safety data reported in the Marketing Authorisation Application.

The inspections revealed several flawed GCP findings, including significant deficiencies in relation to the availability of source data at the investigator sites, availability of the clinical database, collection and reporting of safety data as well as the investigational medicinal product delivery.

A GCP compliant conduct of the two inspected pivotal trials therefore could not be confirmed for these areas of trial conduct and the safety data reported in the clinical study reports were not recommened for assessment.

- Tabular overview of clinical studies

Clinical pharmacology programme

Clinical Trial No.	Type of Clinical Study
Bioavailability and Bioequivalence Studies	
RC-1291-102	PK and biologic activity; oral solutions and capsules
RC-1291-105	CYP3A4 inhibition, PK and food effects with 25 mg capsules in fed (high-fat meal) and fasted conditions, and interactions with CYP3A4 inhibitor ketoconazole
RC-1291-108	PK study with/without pantoprazole using 25 mg anamorelin free base capsules and 25 mg anamorelin HCl capsules
RC-1291-109	Relative bioavailability of 50 mg tablets and 25 mg capsules and

Clinical Trial No.	Type of Clinical Study
	food effects (fasted vs light breakfast)
HT-ANAM-112	Part 1 – single ascending doses to determine MTD (150-400 mg using 50 and 100 mg tablets)Part 2 – bioavailability (100 mg oral vs 10 mg IV) and renal assessment
HT-ANAM-114	Anamorelin HCl 100 mg DDI/PK study with rifampicin (CYP3A4 inducer) and paroxetine (CYP2D6 inhibitor), and with food effect (fed vs fasted) (100 mg tablets)
Clinical Pharmacology Studies in Healthy Subjects	
RC-1291-101	Single ascending dose, PK and safety with 5 and 25 mg capsules
RC-1291-103	^{14}C-Anamorelin HCl 25 mg ADME study
RC-1291-104	Multiple ascending dose, PK and safety with 25 mg capsules, plus evaluation of CYP3A4 probe midazolam (3-6 mg)
RC-1291-105	CYP3A4 inhibition, PK and food effects with 25 mg capsules in fed (high-fat meal) and fasted conditions, and with interaction with CYP3A4 inhibitor ketoconazole
RC-1291-107	Food and age effect PK study with 25 mg capsules
ST-ANAM-110	PK, Safety and Tolerability of 150 mg (50 mg tablets)
HT-ANAM-112	Part 1 – single ascending doses to determine MTD (150-400 mg using 50 and 100 mg tablets) Part 2 – bioavailability (100 mg oral vs 10 mg IV) and renal assessment
HT-ANAM-113	E14 thorough QT, ECG/safety study using 100 mg and 300 mg anamorelin HCl (100 mg tablets)
HT-ANAM-114	Anamorelin HCl 100 mg DDI/PK study with rifampin (CYP3A4 inducer) and paroxetine (CYP2D6 inhibitor), and with food effect (fed vs fasted) (100 mg tablets)
Clinical Pharmacology Studies in Patients	
RC-1291-203/205	Safety, Efficacy, and PK in cancer patients using 50 mg (25 mg capsules)
RC-1291-206	Safety, Efficacy, and PK in cancer patients using 50 or 100 mg (25 mg capsules)
ST-ANAM-207	Safety, Efficacy, and PK in NSCLC patients using 50 or 100 mg (50 mg tablets)
HT-ANAM-301	Anamorelin population PK study in NSCLC patients with 100 mg anamorelin HCl tablets
HT-ANAM-112	Part 1 – single ascending doses to determine MTD (150-400 mg using 50 and 100 mg tablets) Part 2 – bioavailability (100 mg oral vs 10 mg IV) and renal assessment
HT-ANAM-113	E14 thorough QT, ECG/safety study using 100 mg and 300 mg anamorelin HCl (100 mg tablets)

Clinical efficacy studies pertinent to the claimed indication

Study ID **Country**	**Study Design and primary endpoint and main inclusion criteria**	**Treatment Groups,** **No. of Subjects (by Treatment Group)**	**Demographics**	**Study Start, End / Status (Available results)**
Phase 2 trials				
RC-1291-203/205 RC-1291-203: USA	Study Phase: Phase 2 Study design: multi-centre, randomized,	N = 82 RC-1291-203: N = 16	82 subjects (51 males and 31 females) 19-94 years of	Study start date: 29 June 2005 (Study 203)

(7 centres) RC-1291-205: USA (18 centres)	double-blind, placebo-controlled, multiple-dose *RC-1291-203:* cross-over phase (2x 3d), parallel phase (12 weeks) *RC-1291-205:* parallel phase (12 weeks), open label extension (4 weeks) key efficacy endpoints: changes in LBM by DEXA, changes in HGS of non-dominant hand, changes in IGF-1 and IFGBP-3, change in QoL by ASAS main inclusion criteria: patients with cancer anorexia/cachexia defined as involuntary loss of at least 5% of body weight over the preceding 6 months	*cross-over phase (randomized):* anamorelin 50mg QD over 3 consecutive days and placebo for 3 consecutive days or vice versa with 3-7 day wash-out phase in-between *parallel phase (randomized):* anamorelin 50mg QD or placebo for 12 weeks RC-1291-205: N = 66 *parallel phase (randomized):* anamorelin 50mg QD or placebo for 12 weeks *open-label extension:* anamorelin 50mg QD for 4 weeks	age	study completion date: 26 Oct 2006 (study 205) Status: completed
RC-1291-206 USA (17 centres)	Study Phase: Phase 2 Study design: multi-centre, randomized, double-blind, placebo-controlled, multiple-dose, parallel group *Part A:* parallel group (4 weeks) *Part B:* active treatment extension, uncontrolled (8 weeks) primary efficacy endpoint: body weight gain at day 29 main inclusion criteria: advanced histologically diagnosed cancer and cancer anorexia/Cachexia defined as follows: involuntary loss of at least 5 lb (2.27 kg) o body weight occurring within the preceding 6 months	N = 53 *Part A (randomized):* N = 53 anamorelin 50mg, anamorelin 100mg or placebo QD for 28 days *Part B (extension):* N = 39 anamorelin 50mg (continued from part A) or anamorelin 100mg (continued from part A and placebo patients in part A) QD for 56 days	53 subjects (31 males and 22 females) 44-88 years of age	Study start date: 16 Aug 2006 study completion date: 26 Apr 2007 Status: completed
ST-ANAM-207 USA, India (21 centres)	Study Phase: Phase 2 Study design: multi-centre, randomized,	N = 228 (2 subjects never received treatment)	226 subjects received treatment (171 males and 55	Study start date: 15 May 2008 study

	double-blind, placebo-controlled, multiple-dose, parallel-group co-primary endpoint: change from baseline in HGS of the non-dominant hand and change from baseline in body weight main inclusion criteria: previously untreated and histologically or cytologically documented "wet" stage IIIB or stage IV NSCLC and candidates for treatment with the carboplatin/paclitaxel (+/- bevacizumab) regimen	*3 treatment arms (randomized):* anamorelin 50mg (N = 76), anamorelin 100mg (N = 73) or placebo (N = 77) QD for 12 weeks	females) 25-80 years of age	completion date: 27 Sep 2011 Status: completed
Phase 3 trials				
HT-ANAM-301 (ROMANA 1) Belarus, Belgium, Canada, Czech Republic, France, Germany, Italy, Netherlands, Poland, Russia, Serbia, Slovenia, Spain, Ukraine, USA (62 centres open, 54 centres screened patients)	Study Phase: Phase 3 Study design: multicentre, randomized, double-blind, placebo-controlled, parallel-group co-primary endpoint: change from baseline in LBM as measured by DEXA over 12 weeks and change from baseline in HGS of the non-dominant hand over 12 weeks main inclusion criteria: histologic or cytologic diagnosis of NSCLC (unresectable Stage III or IV) and cachexia (defined as an involuntary weight loss of ≥ 5% within 6 months prior to screening or a BMI < 20 kg/m²)	N = 484 *2 treatment arms (randomized):* anamorelin 100mg (N = 323) or placebo (N = 161) QD for 12 weeks	484 subjects (368 males and 116 females) 30-86 years of age	Study start date: 08 Jul 2011 study completion date: 28 Jan 2014 Status: completed
HT-ANAM-302 (ROMANA 2) Australia, Hungary, Israel, Poland, Russia, UK, USA (50 centres open, 39 centres screened patients)	Study Phase: Phase 3 Study design: multicentre, randomized, double-blind, placebo-controlled, parallel-group co-primary endpoint: change from baseline in LBM as measured by DEXA over 12 weeks and change from baseline in HGS of the non-dominant hand over 12 weeks	N = 495 *2 treatment arms (randomized):* anamorelin 100mg (N = 330) or placebo (N = 165) QD for 12 weeks	495 subjects (362 males and 133 females) 33-88 years of age	Study start date: 14 Jul 2011 study completion date: 31 Oct 2013 Status: completed

	main inclusion criteria: histologic or cytologic diagnosis of NSCLC (unresectable Stage III or IV) and cachexia (defined as an involuntary weight loss of ≥ 5% within 6 months prior to screening or a BMI < 20 kg/m²)			
HT-ANAM-303 (ROMANA 3) Australia, Belarus, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, Russia, Serbia, Slovenia, Spain, Ukraine, USA (82 centres open, 70 enrolled patients)	Study Phase: Phase 3 extension study of HT-ANAM-301 or HT-ANAM-302 Study design: multicentre, randomized, double-blind, placebo-controlled, parallel-group efficacy parameters: change in body weight, change in HGS, QoL assessed by scores within FAACT and FACIT-F main inclusion criteria: patients who completed dosing in either of the studies HT-ANAM-301 or HT-ANAM-302 were able to enrol in this study and continue to receive the study drug to which they were assigned (anamorelin 100mg or placebo QD) for an additional 12 weeks	N = 513 *2 treatment arms (continuation from HT-ANAM-302 + -303):* anamorelin 100mg (N = 345) or placebo (N = 168) QD for 12 weeks	513 subjects (387 males and 126 females) 36-88 years of age	Study start date: 14 Nov 2011 study completion date: 22 Apr 2014 Status: completed

2.4.2. Pharmacokinetics

The applicant submitted a comprehensive clinical pharmacology program. This included 12 Phase 1 studies and a Phase 3 population PK study. Supportive PK data from four Phase 2 studies in subjects with cancer or NSCLC anorexia-cachexia are also included.

- **Absorption / Bioavailability**

The key parameters of anamorelin have been derived. Absolute oral bioavailability of anamorelin HCl was determined as approximately 37%. The low bioavailability is in line with the BCS Class III classification. Following administration of Adlumiz 100 mg tablets, anamorelin absorption is rapid with peak plasma concentrations occurring at approximately 0.7 to 1 hour after administration.

Although there is a high degree of variability, there does appear to be a difference in exposure across the phase I studies (e.g the 90% CI free base versus HCL does not contain 1).

- **Bioequivalence**

Comparative BE was evaluated between the early-development 25 mg capsule and phase IIb-50 mg tablet formulations. However, all confidence intervals for AUC and C_{max} tablet/capsule-ratios were

lower than the recommended BE margins of 80-125%, the phase IIb tablet formulation cannot be regarded bioequivalent to the capsule formulation.

Low permeability of anamorelin, as a BCS-class III-characteristic, with the involvement of an active efflux transporter, identified as P-gp, was established.

- **Influence of food**

Food decreases the bioavailability of anamorelin and both AUC and Cmax is 18% are lower in the fed state compared to fasting. Also the presence of food delayed the peak time (Tmax). Results from another food-effect study showed a marked decrease of C_{max} and AUC also when taken 2 hours after a meal. As a result, Anamorelin is recommended to be taken without food and at least one hour before a meal.

- **Distribution / Protein binding**

Anamorelin is approximately 97% to 98% bound to plasma proteins predominantly to alpha-1 acid glycoprotein. Anamorelin is widely distributed throughout the body and efficiently eliminated mainly by metabolism. The volume of distribution (Vz/F) and the systemic clearance (CL/F), estimated after administration of the final formulation of 100 mg tablets, ranged respectively from 305 to 468 L (4.19 - 6.22 L/kg) and from 52 to 68 L/h (0.63 - 0.85 L/h/kg) in healthy subjects.

Metabolism / Elimination

For elimination half-life $t_{1/2}$, a bi-exponential decline with a range between 6.28 and 24.6 hours was described.

The major route of elimination of anamorelin from the body was the faeces. Even though the drug is 37% bioavailable, yet the parent compound accounts for approximately >85% of the total peak area in the faecal extracts. Therefore, it also appears that a significant proportion of the parent drug is eliminated via biliary excretion. Urine concentrations of anamorelin (~1% to 7% anamorelin excreted unchanged) and renal clearance were low, indicating that renal excretion of anamorelin is a minor elimination pathway. However, setting the renal excreted fraction in relation to that absorbed then the renal pathway increases to ~22% of total elimination as a worst case estimation.

In a human radio-labelled study, nearly 100% of total circulating radioactivity over 24 hours was recovered. The majority of the dose was recovered in faeces (92% to 93%) unchanged confirming that renal excretion is a very minor route of elimination. Two predominant metabolites (i.e., M4 and M6) and two minor metabolites (i.e. M3 and M11) were excreted in faeces. The contribution of metabolites M4 and M6 to overall drug activity of anamorelin can be considered negligible.

- **Dose proportionality and time dependency**

Accumulation of anamorelin after repeated dosing is minimal. Primary PK parameters show that PK of anamorelin was linear on multiple dosing. At supra-therapeutic doses between 150-400mg AUC and Cmax increased overproportionally. There is no evidence of time dependency.

- **Intra- and inter-individual variability**

Inter-subject variability was moderate to high both in healthy volunteers and in cancer patients. PopPK simulations predicted an inter-subject variability of %CV for C_{max} 63.6%, AUC0-24 52.3%, t_{max} 73.0%, and CL/F 63.1% from 6 studies, 2 of which performed in cancer patients.

- **Special populations**

Based on the low renal excretion the applicant did not consider the need of conducting a clinical study in subjects with renal impairment, this is supported by data from the POPPK analysis.

Anamorelin undergoes hepatic metabolism as evidenced by in vitro studies, and is primarily metabolized by CYP3A4 (which should be investigated for polymorphisms). Anamorelin metabolism occurs mainly through a combination of cytochrome-mediated monooxygenation and N-demethylation, leading to the formation in vivo of oxidative and or demethylated metabolites (primarily M3, M4, M6, and M11) and one conjugated metabolite (M12).

The PK of anamorelin in elderly (no subjects reported to be 85+ years) appears to be comparable to that of patients <65 years.

Under comparison with external data of healthy young males, in healthy volunteers an obvious gender-related difference in PK parameters was observed with the early 25mg capsule formulation, where females obviously had a higher exposure and plasma concentration per dose of anamorelin (~1.8-1.9-fold higher). On the contrary, estimations from a popPK analysis for the 70 cancer cachexia/anorexia patients (15 female, 55 male of study HT-ANAM-301) with the 100 mg tablet formulation did not indicate gender related differences; however, patient sample data in the popPK model are too sparse to draw valid conclusions whether a relevant gender effect is evident or not. However, in view that no clinically relevant safety differences were observed, the higher exposure in females was not considered a concern.

- **Interactions**

The current *in vitro* study shows that anamorelin is a substrate for MDR1 and OATP1B3, so a possible *in vivo* interaction with perpetrator drugs against these two transporters could be considered likely.

The ability of anamorelin HCl to induce the messenger ribonucleic acid (mRNA) expression and/or activity of CYP2B6 and CYP3A4 was provided.

Concomitant administration of anamorelin HCl did not produce a meaningful effect on the PK of orally administered midazolam, a CYP3A4 probe molecule. When co administered with ketoconazole (a strong CYP3A inhibitor) clinically meaningful differences in anamorelin PK parameters were observed after anamorelin HCl administration. The mean Cmax and AUC0-∞ were approximately 3.1-fold and 3.2-fold higher, respectively, with concomitant ketoconazole than without it. Given that anamorelin is a P-gp substrate and that ketoconazole is both a CYP3A4 and P-gp inhibitor, it cannot be excluded that the interaction is due to both CYP3A4 and P-gp inhibition, and not CYP3A4 inhibition alone.

It is concluded that there is a significant DDI with the CYP3A4 inducer rifampin, such that anamorelin HCl administration post-rifampin results in decreased bioavailability.

M4 and M6 metabolites were found in low concentrations when compared to the parent anamorelin, regardless of exposure to rifampin. The metabolite to parent ratios for both M4 and M6 indicate that they are not classified as major metabolites (<10%).

It was also concluded that anamorelin maximum concentrations (Cmax) were significantly higher following anamorelin HCl administration post-paroxetine versus the fasted condition (28% or 1.3-fold increase). However, overall exposure to anamorelin (i.e., AUC0-∞) was 15% lower post-paroxetine compared to the fasted state (1.2-fold decrease); this difference was suggestive but not statistically significant. The variability in drug exposure and concentrations was high. Overall, the data suggest that CYP2D6 inhibition does not cause a clinically meaningful interaction.

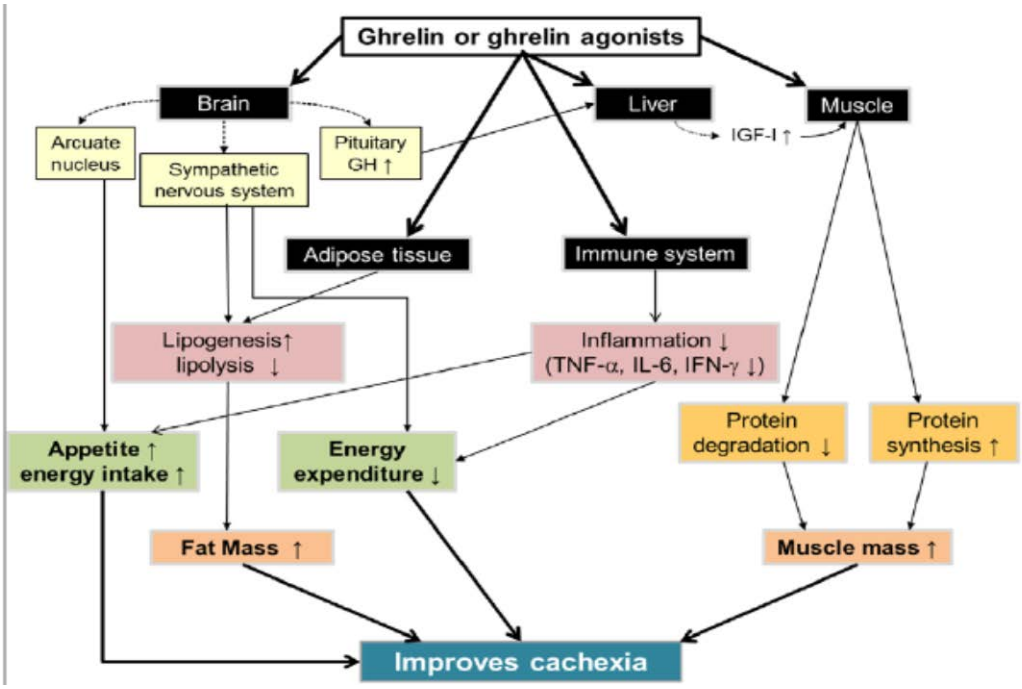
2.4.3. Pharmacodynamics

Anamorelin is a ghrelin agonist with high affinity at the growth hormone secretagogue (GHS)-receptor, with an in vitro EC_{50} = 1.5 nM. As a ghrelin agonist its primary pharmacodynamic effects are

considered a stimulation of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) secretion, both of which may be utilised and measured as the main pharmacodynamic biomarkers, as well as insulin growth factor binding protein (IGFBP-3). Secondary pharmacodynamics effects are expected to be an increase of appetite and muscle mass, the latter measured as lean body mass (LBM) and body weight.

Ghrelin acts in the brain to regulate food intake, body weight, adiposity, and glucose metabolism. Ghrelin modulates systemic metabolism via activation of orexigenic neural circuits. Numerous central and peripheral actions of ghrelin have been described, including stimulation of gut motility and gastric acid secretion, modulation of sleep, taste sensation and reward seeking behavior, regulation of glucose metabolism, suppression of brown fat thermogenesis, modulation of stress and anxiety, protection against muscle atrophy and improvement of cardiovascular functions such as vasodilatation and cardiac contractility. Ghrelin levels rise pre-prandially, and administered ghrelin reliably increases food intake in humans and rodents, supporting a role for ghrelin in hunger, meal initiation, and feeding behavior in normal physiology. The surge in ghrelin before a meal could be linked to another role for ghrelin i.e. to prepare the organism for incoming food in order to metabolize and store energy efficiently.

Figure 4. Biological rationale for the pharmaocologic use of ghrelin agonist in cachexia



- **Primary pharmacology**

The proposed biological activity of anamorelin HCl in terms of primary pharmacodynamic effects was studied and proofed in phase I studies in healthy volunteers, where significant increases in serum GH, IGF-1 and IGFBP-3 secretion were observed with doses ≥25 mg, consistent with anamorelin's activity as a ghrelin receptor agonist. A split-dose regimen of 2x25mg bid provided no different response compared to a 50mg QD administration. However, the applicant did not discuss whether plasma concentration C_{max} or exposure AUC of anamorelin is relevant for the pharmacodynamic effects on the biomarkers GH, IGF-1 and IGFBP-3.

Similar pharmacodynamic activity of 25mg on GH response was observed regardless of gender, although in the same study the anamorelin plasma concentration and exposure were higher in females. A lower GH secretion was observed in elderly, consistent with what can be expected as the physiological attenuated response.

In cancer patients with cachexia the anamorelin effects on IGF-1 and IGFBP-1 indicated a dose dependent increase between 50mg and 100mg, however the confirmation for dose-dependency of effects on IGFBP-1 in NSCLC patients is considered not fully established.

Evaluation of other possible pharmacodynamic targets was also evaluated and revealed negligible effects on other pituitary axis hormones or insulin at doses up to 75mg.

- **Secondary pharmacology**

The proposed biological activity of anamorelin HCl in terms of secondary pharmacodynamic effects was mainly studied by measurement of body weight or lean body mass in healthy volunteers and cancer patients.

While increases in appetite and caloric food intake were observed at doses of 25mg and above in healthy volunteers, an obvious difference in effect size and hence a dose dependency for 50mg and 100mg doses is considered not unequivocally established from the phase II studies in cancer patients for this pharmacodynamic marker. Even worse, in a cancer population with anorexia/cachexia even inverted effect sizes on body weight between the 50mg and 100mg doses were measured.

- **Safety pharmacology including Thorough QT study**

A thorough QT study ((HT-ANAM-112) was performed. In this study it was expected to use 400mg as the supra-therapeutic dose, since clinical data of study HT-ANAM-112 has shown this to be the MTD with clinically acceptable effects on QRS changes and it would cover the >3-fold increases of C_{max} and AUC with strong CYP3A4 inhibitor interactions.

However, due to an unexpected high QRS interval widening in one subject in the first period, with maximum mean QRS change from baseline of 87ms (~90% increase from baseline), the initial cohort of 30 patients was completely terminated and the study was amended (amendment No. 3) to re-start with 60 new patients with 300mg as the supra-therapeutic dose.

100mg anamorelin did not lengthen the QTcF interval as extensively as the positive control moxifloxacin; however, the upper bound of the 2-sided 90% CI was beyond the regulatory threshold of 10ms. In contrast, the supra-therapeutic 300mg dose showed an increased change from baseline, even higher than the positive control at 4 hours post-dose.

2.4.4. Discussion on clinical pharmacology

Due to the fact that several relevant PK studies were performed with lower anamorelin doses and the early capsule formulation, it is difficult to extrapolate the results from these studies to the current formulation.

As all confidence intervals for AUC and C_{max} tablet/capsule-ratios were lower than the recommended BE margins of 80-125%, the phase IIb tablet formulation cannot be regarded bioequivalent to the capsule formulation. Therefore, the PK parameters obtained for the capsule formulation, could not be directly extrapolated to the 50 g tablet and the 100mg tablet, also in view of the non-linear PK at supra-therapeutic doses.

The CHMP considered that the need for a bridging BE study between the 100mg phase III/proposed commercial tablet and the 50mg phase II tablet could be waived if *in vitro* data showed sufficient comparable release between both formulations. However, as such comparative dissolution profiles were not submitted it could not be demonstrated that the requirements of the BE guideline were fulfilled to grant a biowaiver.

The intended target population of cachexia in non-small lung cancer patients are likely to receive CYP3A4 inducers or inhibitors concomitantly to anamorelin. The Applicant proposed to state in section 4.5 of the SmPC that Co-administration of anamorelin with medicinal products that inhibit (e.g., ketoconazole) or induce (e.g., rifampin) CYP3A4 activity may affect anamorelin plasma concentrations. In addition, a contraindication for CYP3A4 inhibitors was also included in the proposed SmPC.

The CHMP noted that even though anamorelin undergoes hepatic metabolism no clinical study was conducted in hepatic impaired subjects. Although the present limited data did not indicate a clinically relevant correlation between exposure and variable degrees of hepatic function it would be beneficial to understand and quantify the impact of the hepatic status on anamorelin exposure.

Based on its proposed nature and mode of action as a ghrelin receptor agonist, stimulation of growth hormone and IGF-1 secretion were expected as the pharmacodynamic responses, which would lead to secondary pharmacodynamic effects like increase of appetite and muscle mass, the latter measured as lean body mass (LBM) and body weight.

At doses of 25 mg and above PD responses in terms of primary and secondary pharmacological markers were measured in healthy volunteers and patients. It remains unclear whether plasma concentration or exposure is relevant for PD effects, as a definite dose finding is considered not established from the study results. Nevertheless, the applicant decided to further develop the 100 mg dose.

Due to its nature as a sodium and hERG channel blocker, a thorough QT study against moxifloxacin was performed, which established anamorelin's cardiac sodium channel blocking potential. While QTcF was only slightly affected, PR and QRS intervals were significantly prolonged, at least at doses >100mg. Cardiac effects seem independent from maximal plasma concentrations, which makes their timely clinical assessment in real life difficult. To be able to better quantify these effects, a comparative study against a class I antiarrhythmic would be necessary.

2.4.5. Conclusions on clinical pharmacology

Even though the pharmacokinetics of anamorelin were thoroughly investigated, there are still some questions which could be important in supplementing the current knowledge on the pharmacological properties of anamorelin.

These relate to the impact of hepatic impairment in anamorelin exposure levels, better quantifying the potential of anamaorelin to block cardiac Na+ currents to and a bridging study BE study or (comparative in vitro dissolution data) between the 100mg phase III/proposed commercial tablet and the 50mg phase II tablet. Even though the applicant is recommended to continue addressing these uncertainites, the CHMP considered that if efficacy and safety could be confirmed these could be addressed in the SmPC by necessary warnings and precautions and possibly further post-authorisation activities.

2.5. Clinical efficacy

2.5.1. Dose response studies

Three Phase 2 studies (including studies 203 and 205 which have been combined into a single CSR) were submitted to support the hypothesis that anamorelin represents a potential treatment of anorexia-cachexia in subjects with advanced solid malignancies, including NSCLC.

Study RC-1291-203/205

Study RC-1291-203/205, enrolled 82 subjects with various cancer types and involuntary loss of at least 5% of body weight over the preceding 6 months. Subjects were randomized to either placebo or anamorelin HCl 50 mg for up to 12 weeks.

As this study demonstrated positive findings on lean body mass (p=0.0006) without any clinically meaningful dose-limiting toxicities, a higher dose of 100 mg anamorelin HCl was examined in subsequent Phase 2 studies and compared to the 50 mg dose. The observed increases in lean body mass were highly correlated with changes in total body mass (p=0.0001). Statistically significant treatment effects were also seen as increases in biochemical markers of IGF-1 (p=0.0001) and IGFBP-3 (p=0.0002) for the same period as well.

Handgrip strength also increased over baseline when compared to placebo in a statistically significant manner (p=0.014). None of the QoL measures were significant at week 12 and only one (ASAS) was significantly better at one time point (week 4).

Study RC-1291-206

Subjects (N= 53) with various cancer types and involuntary loss of at least 2.27 kg (5 pounds) of body weight over the preceding 6 months were enrolled in this study and randomized to either placebo, anamorelin HCl 50 mg, or anamorelin HCl 100 mg for 4 weeks. The study had a parallel double blind, placebo-controlled treatment period, followed by an 8-week open-label active treatment extension.

Anamorelin treatment effect on the overall body weight change through the 4-week period was statistically significant at each dose level and the combined dose group when comparing with the placebo treatment (50 mg /day: difference =1.5 kg, 95%CI: 0.6 – 2.4, p=0.0015; 100 mg/day: difference = 1.14 kg, 95%CI: 0.3 – 1.9, p=0.0070; combined doses: difference = 1.32 kg, 95%CI: 0.6 – 2.1, p=0.0011).

Subjects in the anamorelin 50 mg/day treatment group lost a small amount of weight from Week 4 to Week 12 (mean change, -0.73 kg), whereas subjects receiving 100 mg/day continued to gain a small amount of weight from Week 4 to Week 12 (mean change, +0.39 kg). In addition, the subjects who were switched from placebo to anamorelin 100 mg/day gained a mean of 0.5 kg from Week 4 to Week 12.

The effects of anamorelin 50 mg/day and 100 mg/day on biochemical markers of drug activity (IGF-1 and IGFBP-3) were significant at all time points assessed during the parallel double blind phase. The effects were maintained during the open-label extension phase, but no further increases in IGF-1 or IGFBP-3 were observed from Week 4 to Week 12 in either of the active groups.

Other efficacy endpoints, such as handgrip strength, cancer symptom, appetite, and disease-specific quality of life instruments, hormonal markers and Karnofsky score were investigated but are not presented in detail in this report as they did not show any significant differences between the treatment arms.

Safety was evaluated from reported AEs, abnormal clinical laboratory values, changes in EKG parameters, and changes in vital signs values. Safety variables were summarized descriptively.

ST-ANAM-207

In this study, 226 NSCLC subjects were treated for up to 12 weeks with either placebo, anamorelin HCl 50 mg, or anamorelin HCl 100 mg.

The co-primary efficacy endpoints in this Phase II study were changes from baseline in Body Weight and Hand Grip Strength in the nondominant hand for the MITT population (**Table 10**). In the hierarchy of testing the results of the 100mg had to be assessed first.

Table 10. Repeated measures ANCOVA of 12-Week average anamorelin treatment effect on body weight and handgrip strength of non-dominant hand in the mITT population is study ST-ANAM-207

Endpoint	Statistic	Placebo N=74	Anamorelin 50 mg N=72	Anamorelin 100 mg N=72
Body Weight (BW)				
Baseline	N	74	72	69
	Mean (SE)	56.2 (1.69)	53.9 (1.41)	52.9 (1.39)
	Std	14.50	12.00	11.54
	Median	54.3	52.4	53.3
	Range	32.7, 90.5	29.4, 90.5	31.9, 91.9
12-wk average Observed	N	74	72	69
	Mean (SE)	54.8 (1.64)	53.6 (1.36)	53.1 (1.39)
	Std	14.11	11.52	11.59
	Median	52.5	51.8	52.9
	Range	34.3, 91.1	29.2, 85.3	31.9, 89.0
12-wk average CFB	N	74	72	69
	Mean (SE)	-1.4 (0.30)	-0.3 (0.26)	0.2 (0.30)
	Std	2.57	2.23	2.51
	Median	-0.9	-0.2	0.4
	Range	-9.8, 3.2	-5.3, 6.2	-9.1, 6.9
	LS Mean (SE)[a]	-1.32 (0.346)	-0.30 (0.349)	0.14 (0.359)
	Anamorelin vs. PL		1.02	1.47
	95% CI of Difference		0.207, 1.834	0.655, 2.276
	Nominal p-value[b]		0.0142 (NA)	0.0005 (S)
Handgrip Strength of Non-dominant Hand (HGS)				
Baseline	N	74	72	69
	Mean (SE)	30.7 (1.31)	26.7 (1.12)	28.8 (1.05)
	Std	11.26	9.49	8.74
	Median	29.4	25.9	26.9
	Range	8.9, 64.7	6.0, 53.2	10.5, 49.6
12-wk average Observed	N	74	70	68
	Mean (SE)	28.8 (1.23)	25.8 (1.13)	27.7 (1.02)
	Std	10.62	9.45	8.41
	Median	26.5	24.8	27.3
	Range	11.9, 61.2	4.6, 53.8	12.6, 49.6
12-wk average CFB	N	74	70	68
	Mean (SE)	-1.9 (0.51)	-0.7 (0.45)	-1.0 (0.43)
	Std	4.41	3.73	3.58
	Median	-1.1	-0.6	-0.6
	Range	-13.7, 8.2	-11.7, 6.8	-9.7, 8.3
	LS Mean (SE)[a]	-1.82 (0.592)	-1.27 (0.598)	-1.25 (0.627)
	Anam vs. PL		0.55	0.58
	95% CI of Difference		-0.736, 1.841	-0.692, 1.842
	Nominal p-value[b]		0.3990 (NA)	0.3718 (NS)

Key: ANCOVA = analysis of covariance; MITT = modified intent-to-treat; Std = standard deviation.
CFB = Change from Baseline calculated as (visit value - baseline value).
a LS means were derived from the repeated measures ANCOVA model with unstructured covariance matrix. Differences and corresponding 95% CIs were calculated as (Anamorelin - Placebo).
b Statistical significance of the nominal p-value is subject to the Hochberg Adjustment based on a pre-specified sequence: p-value is statistically significant if both nominal p-values for treatment effect on HGS of the non-dominant hand and BW are ≤0.0490 for 100 mg. Otherwise, the smaller nominal p-value must be ≤0.0245 to be statistically significant. The primary efficacy measures between the anamorelin 100 mg dose and placebo will be tested first, and if significance at the 0.049 level for both primary endpoints is demonstrated, interpretation for statistical inference would then proceed to the anamorelin low dose (50 mg) group vs. placebo family.
S = statistically significant; NS = Not statistically significant; NA = Not Assessed

A single QoL measure, MDASI, was used during the study, despite a number of others being used in the preceding phase II and following phase III trials. Whilst 100mg showed a numerical advantage over placebo at 12 weeks, this was not statistically significant. 50mg was numerically worse than placebo.

The 12-week changes from baseline for IGFBP-3 (biochemical marker of drug activity) were significant compared with placebo for both the 50 mg and 100 mg anamorelin treatment arms (nominal p-value <0.0001 for both treatments). However, the mean concentrations of IGFBP-3 at baseline (3.1 µg/ml

for both groups) as well as at the end of treatment (3.7 µg/ml and 3.9 µg/ml in the 50 mg/day and 100 mg/day, respectively) remained within the normal range.

The main safety objectives of the study were to evaluate the safety and tolerability of anamorelin and the effect of anamorelin HCl on the therapeutic efficacy of chemotherapy as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria and overall survival.

No statistically significant differences in tumor response, including best overall response rate and PFS, were observed among the three treatment arms. The mean duration of response was 100.0, 106.3, and 94.8 days in the placebo, 50 mg, and 100 mg treatment arms, respectively.

The effect of anamorelin 50 mg or 100 mg on overall survival or long-term survival compared to placebo is summarised in **Table 11.**

Table 11. Overall survival in the safety population in Study ST-ANAM-207

	Placebo (N=77)	Anamorelin 50 mg (N=76)	Anamorelin 100 mg (N=73)
N (Censored)	77 (19)	76 (22)	73 (14)
Alive at End of Study	55 (71.4%)	40 (52.6%)	49 (67.1%)
Dropped Out[a]	22 (28.6%)	36 (47.4%)	24 (32.9%)
Died (During or After Study)	58 (75.3%)	54 (71.1%)	59 (80.8%)
KM Estimates			
25th Percentile (95% CI)	129.0 (82.0 to 159.0)	105.0 (60.0 to 146.0)	133.0 (71.0 to 181.0)
50th Percentile (95% CI)	263.0 (190.0 to 350.0)	202.0 (162.0 to 254.0)	234.0 (189.0 to 369.0)
75th Percentile (95% CI)	614.0 (365.0 to 751.0)	364.0 (262.0 to 683.0)	465.0 (384.0 to 605.0)
--- Cox PH Model Analysis ---			
Treatment	HR[b]	1.28	1.11
	95% CI of HR	0.88, 1.86	0.77, 1.59
	p-value[c]	0.1935	0.5814

Source: Section 14, Table 26.2
Key: CI = confidence interval; HR = hazard ratio
a Dropped out counts include subjects who died on study (N=28). Censored numbers include patients lost to followup (N=43) as well as those still alive (N=12).
b Hazard ratios for Anamorelin vs Placebo derived from a stratified Cox proportional hazards model with randomization stratum as the strata variable.
c p-values are from the Wald's chi-square test.

No difference in hand grip strength, the other co-primary endpoint, was observed between the three treatment arms (data not shown).

2.5.2. Main studies

The efficacy of anamorelin in subjects with advanced NSCLC and cachexia has been evaluated in two Phase 3 studies, followed by a 12-week safety extension study. As these studies are comparable in design and methods, except for the fact that population pharmacokinetics and time-matched post-dose ECGs were only performed in study HT-ANAM-301, the studies are presented together in the following sections.

HT-ANAM-301 (ROMANA 1) and HT-ANAM-302 (ROMANA 2)

ROMANA 1 and ROMANA 2 were international, multicentre, 2:1 randomized, double-blind, placebo-controlled, phase 3 clinical studies in patients with 'documented histologic or cytologic diagnosis of Stage III or IV NSCLC (stage III patients must have had unresectable disease)' and 'involuntary weight loss of ≥ 5% body weight within 6 months prior to screening or a screening BMI < 20 kg/m^2'.

Methods

Study Participants

Main inclusion criteria for studies ROMANA 1 and 2

1. Females and males at least 18 years of age.

2. Documented histologic or cytologic diagnosis of American Joint Committee on Cancer Stage III or IV NSCLC. Stage III patients must have had unresectable disease.

3. With regard to chemotherapy and/or radiation therapy:

   - Patients may have been receiving maintenance chemotherapy.

   - Patients planning to initiate a new chemotherapy and/or radiation therapy regimen may have done so only within ± 14 days of randomization.

   - Patients may have completed a chemotherapy and/or radiation therapy and/or have no plan to initiate a new regimen within 12 weeks from randomization. At least 14 days must elapse from the completion of the chemotherapy and/or radiation therapy prior to randomization.

4. Involuntary weight loss of ≥ 5% body weight within 6 months prior to screening or a screening BMI < 20 kg/m^2. Weights may have been measured or obtained and documented by patient history.

5. BMI ≤ 30 kg/m^2.

6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.

7. Estimated life expectancy of > 4 months at the time of screening.

8. Adequate hepatic function, defined as aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤ 5× upper limit of normal (ULN).

9. Adequate renal function, defined as creatinine ≤ 2× ULN, or calculated creatinine clearance > 30 ml/minute.

10. The patient was able to understand and comply with the procedures for the HGS evaluation.

11. If the patient was a woman of childbearing potential or a fertile man, he/she must have agreed to use an effective form of contraception during the study and for 30 days following the last dose of

study drug (an effective form of contraception was abstinence, a hormonal contraceptive, or a double-barrier method).

12. The patient must have been willing and able to give signed informed consent and, in the opinion of the Investigator, to comply with the protocol tests and procedures.

Main exclusion criteria for studies ROMANA 1 and 2

1. Other forms of lung cancer (e.g., small cell, mesothelioma).
2. Women who were pregnant or breast-feeding.
3. Known human immunodeficiency virus, hepatitis (B and C), or active tuberculosis.
4. Had major surgery (central venous access placement and tumour biopsies were not considered major surgery) within 4 weeks prior to randomization. Patients must have been well recovered from acute effects of surgery prior to screening. Patients should not have had plans to undergo major surgical procedures during the treatment period.
5. Currently taking prescription medications intended to increase appetite or treat weight loss; these included, but were not limited to, testosterone, androgenic compounds, megestrol acetate, methylphenidate, and dronabinol.
6. Patients unable to readily swallow oral tablets. Patients with severe GI disease (including esophagitis, gastritis, malabsorption, or obstructive symptoms) or intractable or frequent vomiting were excluded.
7. Had an active, uncontrolled infection.
8. Had uncontrolled diabetes mellitus.
9. Had untreated clinically relevant hypothyroidism.
10. Had known or symptomatic brain metastases.
11. Patients receiving strong CYP3A4 inhibitors within 14 days of randomization.
12. Patients receiving tube feedings or parenteral nutrition (either total or partial). Patients must have discontinued these treatments for at least 6 weeks prior to Day 1 and throughout the study duration.
13. Other clinical diagnosis, ongoing or intercurrent illness that in the Investigator's opinion would have prevented the patient's participation.
14. Had previous exposure to anamorelin HCl.
15. Patients who were actively receiving a concurrent investigational agent.

The diagnostic criteria for cachexia used in these studies (involuntary weight loss of $\geq$ 5% body weight within 6 months prior to screening or a screening BMI < 20 kg/m^2) are based on the consensus definition by Fearon et al published February 2011 in Lancet Oncology [Weight loss $\geq$ 5% over past 6 months (in absence of simple starvation); or BMI <20 kg/m^2 and any degree of weight loss >2%; or appendicular skeletal muscle index consistent with sarcopenia (males <7·26 kg/m^2; females <5·45 kg/m^2) and any degree of weight loss >2%] but not identical.

Treatments

Eligible patients were randomized in a 2:1 ratio to anamorelin HCl 100 mg or placebo, taken orally QD for a total of 12 weeks. Study drug was packaged in blister cards. Patients were instructed to take 1 tablet of study drug per day at least 1 hour before the first meal of the day.

Objectives

The primary objectives of the studies were:

· To evaluate the effect of anamorelin HCl on LBM as measured by DXA

· To evaluate the effect of anamorelin HCl on muscle strength as measured by HGS.

The secondary objectives of the study were:

· To evaluate the effect of anamorelin HCl on body weight,

· To evaluate the effect of anamorelin HCl on quality of life as assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and the Functional Assessment of Anorexia/Cachexia Treatment (FAACT),

· To evaluate the effect of anamorelin HCl on overall survival.

The exploratory objectives of the study were:

· To evaluate the effect of anamorelin HCl on quality of life as assessed using the Hunger Assessment Scale,

The safety objective of the study was:

· To evaluate the safety and tolerability of anamorelin HCl.

Outcomes/endpoints

Co-primary endpoints:

- Change in LBM from baseline as measured by DEXA over 12 weeks, and
- Change in HGS of the non-dominant hand from baseline over 12 weeks (the highest value of the 3 measurements of the non-dominant hand was used for the co-primary efficacy endpoint).

For the co-primary efficacy endpoints, the change from baseline “over 12 weeks” was defined as the average of the change from baseline at Week 6 and change from baseline at Week 12.

Key secondary endpoints

(specified in the SAP based on the clinical importance to the co-primary endpoints; there was no type I error control):

- Overall survival for studies HT-ANAM-301 and HT-ANAM-302 pooled
- Quality of life as assessed by the change from baseline over 12 weeks for the following scores within the FAACT and FACIT-F:

- A/CS (additional concerns subscale of the FAACT);
- SEA (newly developed subscale of A/CS);

- Fatigue domain (additional concerns subscale of FACIT-F);
- SEF (newly developed subscale of fatigue domain (3 items) and FACT-G (1 item)).

[Note: For the quality of life secondary efficacy endpoints, the change from baseline "over 12 weeks" was defined as the mean change of the quality of life scores from baseline to Weeks 3, 6, 9, and 12 estimated using pattern-mixture models.]

Other secondary efficacy endpoints:

- Changes in body weight from baseline to Weeks 3, 6, 9, and 12;
- Overall survival during 12-month follow-up period in this study (i.e., for 12 months from randomization);
- Quality of life as assessed by the change from baseline over 12 weeks for the following scores within the FAACT and FACIT-F:
- FAACT and FACIT-F TOI scores;
- FAACT and FACIT-F total scores

[Note: For the quality of life secondary efficacy endpoints, the change from baseline "over 12 weeks" was defined as the mean change of the quality of life scores from baseline to Weeks 3, 6, 9, and 12 estimated using pattern-mixture models.]

- Percentage change from baseline over 12 weeks in LBM;
- Percentage change from baseline over 12 weeks in HGS of the non-dominant hand; and
- Change in HGS of the dominant hand from baseline to Weeks 6 and 12 (the highest value of the 3 measurements of the dominant hand was used).

Sample size

The primary endpoints for the studies were the change from baseline in LBM and the change in HGS. The sample size was estimated based upon a 2 sample t-test with a difference in mean change in HGS from baseline between the anamorelin group and the placebo group of 2.0 kg, assuming a standard deviation of 4.9 kg, using a 2-sided significance level of 0.05.

With a power of 90%, 288 patients (per study) were required based on a 2:1 randomization ratio. With 288 patients, the study had more than 90% power to detect a 2.0 kg difference in LBM between the anamorelin group and the placebo group using a 2 sample t-test assuming a standard deviation of 4.0 kg and a 2-sided significance level of 0.05. The sample size of 288 was adjusted to 333 by dividing a factor of 0.864 (the lower bound for the asymptotic relative efficiency of the Wilcoxon rank-sum test vs. the t-test), to account for the non-parametric test for the primary analyses [Hodges-1956]. For these advanced NSCLC patients, based on the Phase 2 studies using anamorelin HCl, there was an approximate 22% dropout rate from patients who either died due to disease progression, discontinued from the study due to disease progression, or discontinued from the study due to unacceptable toxicity from their ongoing chemotherapy (12% death due to disease progression, 6% due to disease progression, and 4% due to unacceptable toxicity from the ongoing chemotherapy). An additional 8% of patients were expected to discontinue from the study due to other reasons. To accommodate a total 30% dropout rate, a sample size of 477 randomized patients (318 patients in the anamorelin group and 159 patients in the placebo group) was planned (per study).

Randomisation

Central randomization stratified patients by geographic region (North America vs. rest of the world), by chemotherapy and/or radiation therapy status (patients who initiated chemotherapy and/or radiation therapy within ± 14 days of randomization or patients who were only receiving maintenance chemotherapy vs. patients who had no plan to initiate chemotherapy and/or radiation therapy within 12 weeks from randomization), and by weight loss over the prior 6 months (£ 10% of body weight vs. > 10% of body weight).

Blinding (masking)

Both studies were double-blind.

Statistical methods

Studies HT-ANAM-301 and HT-ANAM-302 used the same statistical methods for the analysis of efficacy.

The anamorelin group was claimed to be superior only if both co-primary efficacy tests (LBM and HGS) were rejected in favour of the anamorelin group. The secondary efficacy endpoints were divided into key secondary endpoints and other secondary endpoints: no type I error control was applied to the five key secondary endpoints.

The co-primary efficacy endpoints, change from baseline over 12 weeks in LBM and HGS, were evaluated with a rank-based analysis based on the ITT population, with patients who died prior to Week 12 were first given worse ranks according to their survival time and patients who survived were ranked according to the change in LBM (HGS). Missing data were replaced using multiple imputation under a missing at random (MAR) assumption. The magnitude of treatment effect was expressed as a comparison of the median of the LBM and HGS endpoints between the treatment and placebo arm.

The secondary efficacy analyses were performed based on the MITT Population excluding patients without post-baseline LBM or HGS assessment and the Per-Protocol Population (overall survival was additionally analyzed based on the ITT Population).

Treatment difference for mean change of body weight and PRO measures over 12 weeks was estimated based on a pattern mixture model (with patterns 'Completers', 'Deaths', and 'Drop-outs') applying a repeated measures model with a MAR assumption within pattern. This analysis aims at estimation of the effect if the patients had not died and had not dropped out, and hence had provided a response at week 12. However, it is not agreed that this represents the treatment effect that is of main regulatory interest.

Pooled overall survival (OS) analysis was also evaluated as a secondary endpoint for both Studies HT-ANAM-301 and HT-ANAM-302 combined and completed during a 12 month follow-up period.

Results

Participant flow

Table 12. Patient's disposition in studies HT-ANAM-301 (ROMANA 1) and HT-ANAM-302 (ROMANA 2)

	ROMANA 1			ROMANA 2		
	Placebo n (%)	Anamorelin n (%)	Total n (%)	Placebo n (%)	Anamorelin n (%)	Total n (%)
Randomized	161 (100.0)	323 (100.0)	484 (100.0)	165 (100.0)	330 (100.0)	495 (100.0)
Randomized and not treated	0 (0.0)	3 (0.9)	3 (0.6)	4 (2.4)	0 (0.0)	4 (0.8)
Treated	161 (100.0)	320 (99.1)	481 (99.4)	161 (97.6)	330 (100.0)	491 (99.2)
Completed treatment [1]	118 (73.3)	236 (73.1)	354 (73.1)	119 (72.1)	235 (71.2)	354 (71.5)
Completed the study [2]	121 (75.2)	231 (71.5)	352 (72.7)	118 (71.5)	233 (70.6)	351 (70.9)
Completed the study but did not complete treatment	4 (2.5)	3 (0.9)	7 (1.4)	2 (1.2)	2 (0.6)	4 (0.8)
Discontinued from the study	40 (24.8)	92 (28.5)	132 (27.3)	47 (28.5)	97 (29.4)	144 (29.1)
Death	20 (12.4)	38 (11.8)	58 (12.0)	16 (9.7)	47 (14.2)	63 (12.7)
Withdrawal by patient	10 (6.2)	32 (9.9)	42 (8.7)	23 (13.9)	33 (10.0)	56 (11.3)
Unrelated AE	3 (1.9)	12 (3.7)	15 (3.1)	4 (2.4)	6 (1.8)	10 (2.0)
Study drug-related AE	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.6)	5 (1.5)	6 (1.2)
Other	7 (4.3)	8 (2.5)	15 (3.1)	1 (0.6)	4 (1.2)	5 (1.0)
Lost to follow-up	0 (0.0)	1 (0.3)	1 (0.2)	2 (1.2)	2 (0.6)	4 (0.8)
Patients died during the study (120 days) [3]	35 (21.7)	77 (23.8)	112 (23.1)	35 (21.2)	75 (22.7)	110 (22.2)

Percentage was calculated using the number of patients randomized as the denominator.

1. A patient was considered to have completed treatment if the patient completed at least 11 weeks (77 days) of treatment.
2. A patient was considered to have completed the study if the patient completed the Week 12/Day 85 Visit.
3. Patients who died within 120 days after randomization.

Recruitment

Study HT-ANAM-301- initiation date: 08 July 2011 (first subject enrolled)

completion date: 28 January 2014 (last subject completed)

Study HT-ANAM-302- initiation date: 14 July 2011 (first subject enrolled)

completion date: 31 October 2013 (last subject completed)

Conduct of the study

The protocol for Study HT-ANAM-301 was amended 3 times (twice in sites in Germany and France only, and once globally) and in Study HT-ANAM-302. The main change in these amendments was the deletion of the exclusion of patients who have completed 2 or more prior cytotoxic chemotherapy regimens.

In total, 107 patients in Study HT-ANAM-301 and 99 in Study HT-ANAM-302 had at least 1 major protocol deviation. The most common category of protocol deviations was Study Procedures, including having assessments not conducted at the scheduled visit. None of the protocol deviations reported during the studies impacted the conclusions of safety or efficacy results.

Baseline data

Table 13. Demographic characteristics and baseline (ITT population, Studies HT-ANAM-301 and HT-ANAM-302)

Characterstic Statistic	ROMANA 1			ROMANA 2		
	Placebo N = 161	Anamorelin N = 323	Total N = 484	Placebo N = 165	Anamorelin N = 330	Total N = 495
Age (years) at screening						
N	161	323	484	165	330	495
Mean (SD)	62.6 (8.52)	61.7 (9.65)	62.0 (9.29)	62.8 (9.26)	63.3 (8.25)	63.2 (8.60)
Age group n (%)						
≤ 65 years	105 (65.2)	215 (66.6)	320 (66.1)	108 (65.5)	209 (63.3)	317 (64.0)
> 65 years	56 (34.8)	108 (33.4)	164 (33.9)	57 (34.5)	121 (36.7)	178 (36.0)
Gender n (%)						
Male	121 (75.2)	247 (76.5)	368 (76.0)	122 (73.9)	240 (72.7)	362 (73.1)
Female	40 (24.8)	76 (23.5)	116 (24.0)	43 (26.1)	90 (27.3)	133 (26.9)
Race n (%)						
White	159 (98.8)	319 (98.8)	478 (98.8)	162 (98.2)	326 (98.8)	488 (98.6)
Black or African American	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.6)	2 (0.6)	3 (0.6)
Asian	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.6)	0 (0.0)	1 (0.2)
Native Hawaiian or Other Pacific Islander	-	-	-	0 (0.0)	1 (0.3)	1 (0.2)
other	-	-	-	1 (0.6)	1 (0.3)	2 (0.4)
Missing	2 (1.2)	2 (0.6)	4 (0.8)	-	-	-
Ethnicity n (%)						
Hispanic or Latino	0 (0.0)	13 (4.0)	13 (2.7)	1 (0.6)	1 (0.3)	2 (0.4)
Not Hispanic or Latino	159 (98.8)	308 (95.4)	467 (96.5)	164 (99.4)	329 (99.7)	493 (99.6)
Missing	2 (1.2)	2 (0.6)	4 (0.8)	-	-	-
Weight (kg)						
N	161	323	484	165	330	495
Mean (SD)	67.95 (13.272)	67.58 (12.998)	67.71 (13.077)	62.73 (12.893)	63.94 (13.276)	63.54 (13.149)
Body mass index (kg/m2)						
N	161	323	484	165	330	495
Mean (SD)	23.28 (3.651)	23.15 (3.555)	23.20 (3.584)	22.13 (3.745)	22.52 (3.673)	22.39 (3.698)
Lean body mass (kg)						
N	156	319	475	156	320	476
Mean (SD)	46.041 (8.6782)	45.870 (8.0981)	45.926 (8.2843)	43.591 (8.4076)	43.920 (7.8434)	43.812 (8.0253)
Handgrip strength – non-dominant hand (kg)						
N	157	311	468	164	324	488
Mean (SD)	31.82 (12.076)	32.96 (10.615)	32.57 (11.126)	28.93 (10.551)	28.80 (11.170)	28.84 (10.955)

FAACT total score						
N	159	315	474	161	327	488
Mean (SD)	96.2 (21.12)	96.7 (20.40)	96.5 (20.63)	93.2 (21.15)	91.5 (21.06)	92.1 (21.08)
FAACT A/CS domain score						
N	161	320	481	162	330	492
Mean (SD)	29.9 (8.74)	29.9 (8.37)	29.9 (8.49)	28.8 (8.56)	27.6 (8.78)	28.0 (8.72)
FACIT-F total score						
N	159	314	473	159	324	483
Mean (SD)	97.2 (22.87)	97.6 (22.93)	97.5 (22.89)	93.0 (23.95)	91.4 (23.45)	91.9 (23.61)
FACIT-F fatigue domain score						
N	160	318	478	159	327	486
Mean (SD)	30.9 (10.70)	30.6 (11.13)	30.7 (10.98)	28.6 (10.83)	27.6 (10.67)	27.9 (10.72)

Numbers analysed

Table 14. Data sets analysed Studies HT-ANAM-301 and HT-ANAM-302)

	ROMANA 1			**ROMANA 2**		
	Placebo n (%)	**Anamorelin n (%)**	**Total n (%)**	**Placebo n (%)**	**Anamorelin n (%)**	**Total n (%)**
ITT Population	161 (100.0)	323 (100.0)	484 (100.0)	165 (100.0)	330 (100.0)	495 (100.0)
MITT Population	141 (87.6)	284 (87.9)	425 (87.8)	136 (82.4)	268 (81.2)	404 (81.6)
Per-Protocol Population	133 (82.6)	264 (81.7)	397 (82.0)	130 (78.8)	252 (76.4)	382 (77.2)
Safety Population	161 (100.0)	320 (99.1)	481 (99.4)	161 (97.6)	330 (100.0)	491 (99.2)

Outcomes and estimation

Co-primary endpoints

Table 15. Change in LBM (kg) from baseline over 12 weeks-ITT population, Studies HT-ANAM-301 and HT-ANAM-302

	ROMANA 1		**ROMANA 2**	
time point statistic	**Placebo N = 158**	**Anamorelin N = 316**	**Placebo N = 157**	**Anamorelin N = 321**
Baseline [1]				
Median	46.62	46.31	43.60	43.75
Change from baseline over 12 weeks [2]				
Median (95% CI)	-0.47 (-1.00, 0.21)	0.99 (0.61, 1.36)	-0.98 (-1.49, -0.41)	0.65 (0.38, 0.91)
Treatment comparison vs. placebo				
Median of difference estimate		**1.46**		**1.63**
P-value		< 0.0001		< 0.0001

1. Baseline was defined as the last value obtained prior to the first dose of study drug.

2. *Change from baseline over 12 weeks was defined as the average of the change from baseline at Week 6 and the change from baseline at Week 12.*

Table 16.Change in HGS (kg) of the non-dominant hand from baseline over 12 weeks--ITT population, Studies HT-ANAM-301 and HT-ANAM-302

	ROMANA 1		ROMANA 2	
time point statistic	**placebo N = 158**	**anamorelin N = 316**	**placebo N = 157**	**anamorelin N = 321**
Baseline [1]				
Median	31.80	31.90	28.40	28.00
Change from baseline over 12 weeks [2]				
Median (95% CI)	-1.58 (-2.99, -1.14)	-1.10 (-1.69, -0.40)	-0.95 (-1.56, 0.04)	-1.49 (-2.06, -0.58)
Treatment comparison vs. placebo				
Median of difference estimate		**0.48**		**-0.53**
P-value		0.1475		0.6480

1. *Baseline was defined as the last value obtained prior to the first dose of study drug.*
2. *Change from baseline over 12 weeks was defined as the average of the change from baseline at Week 6 and the change from baseline at Week 12.*

Key secondary endpoints

The "key" secondary endpoints were specified in the SAP based on the clinical importance to the co-primary endpoints.

Pooled overall survival (OS pooled for studies HT-ANAM-301 and HT-ANAM-302)

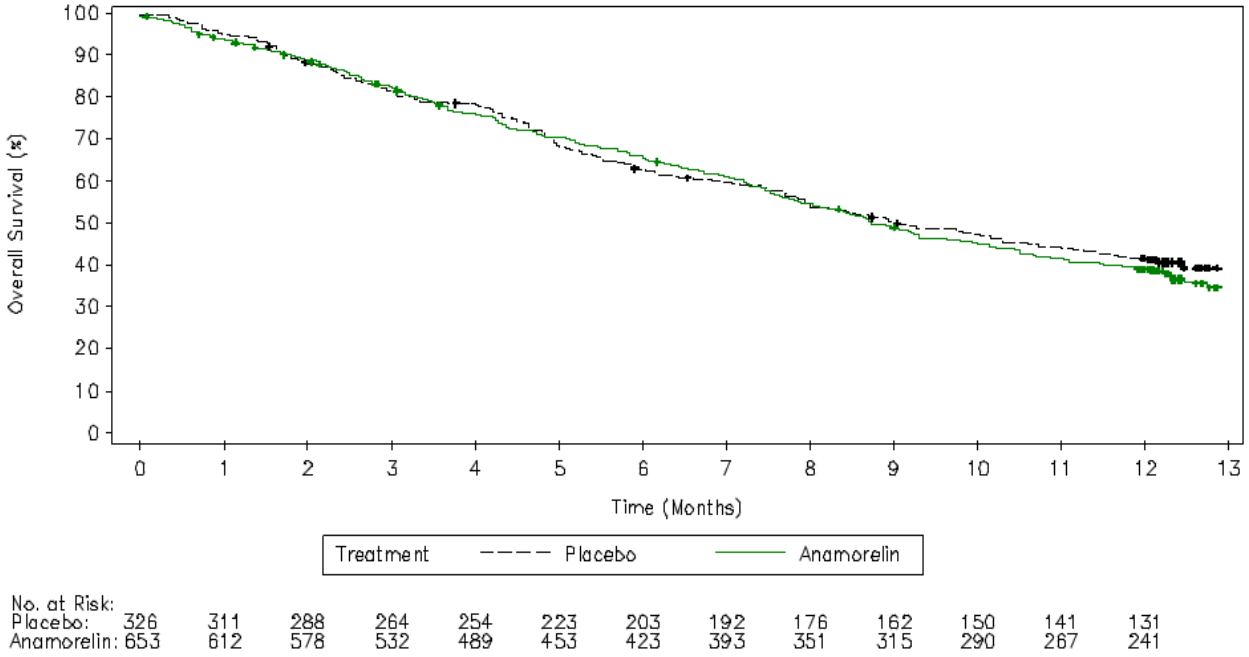
Table 17. Summary of Pooled Overall Survival Study-ITT population studies HT-ANAM-301 and HT-ANAM-302

	Placebo (N = 326)	**Anamorelin**
Number (%) of patients who died	189 (58.0)	393 (60.2)
Died before receiving study drug	4 (1.2)	2 (0.3)
Died during treatment period	34 (10.4)	83
Died during follow-up period	151 (46.3)	308 (47.2)
Number (%) of patients who are	137 (42.0)	260 (39.8)
Overall survival (months)		
Kaplan-Meier Estimate		
Q1	4.50	4.27
Median (95% CI)	9.17 (7.93, 11.00)	8.90 (8.27, 9.80)
Q3	NE	NE
Treatment comparison (anamorelin vs.		
Hazard ratio (95% CI)		1.06 (0.89, 1.26)
Log-rank p-value		0.4691
Rate (%) of being alive for at least [2]		
3 months (95% CI)	81.5 (76.9, 85.3)	82.7 (79.6, 85.4)
6 months (95% CI)	63.2 (57.7, 68.2)	66.1 (62.3, 69.6)
9 months (95% CI)	50.4 (44.8, 55.7)	49.5 (45.5, 53.3)
12 months (95% CI)	42.2 (36.7, 47.5)	39.7 (35.9, 43.4)

Percentage is calculated using the number of patients in the column heading as the denominator. Per protocol, patients are planned to be followed for 1 year from randomization for survival status. Patients who were still alive 12 months + 3 weeks (386 days) after randomization are censored at 12 months + 3 weeks (386 days) in the survival analysis. If the patient died after 12 months + 3 weeks (386 days) of follow-up, the patient was censored to 12 months + 3 weeks (386 days) from the date of randomization.

Hazard ratio and 95% CI were based on Cox proportional hazards model with treatment, geographic region group, chemotherapy or radiation therapy status, and weight loss over prior 6 months as explanatory variables. P-value was obtained from stratified log-rank test based on stratification factors at randomization (geographic region group, chemotherapy or radiation therapy status, and weight loss over prior 6 months).

Figure 5. Kaplan-Meier plot of pooled OS (months) by treatment-ITT population Studies HT-ANAM-301 and HT-ANAM-302



Change in A/CS domain of the FAACT from baseline over 12 weeks

Table 18. Change in A/CS domain score from baseline over 12 weeks-MITT population in Studies HT-ANAM-301 and HT-ANAM-302

	ROMANA 1		ROMANA 2	
time point statistic	**Placebo** **N = 141**	**Anamorelin** **N = 284**	**Placebo** **N = 136**	**Anamorelin** **N = 268**
Overall				
N [1]	141	282	133	266
change from baseline				
LS mean (SE)	1.92 (0.805)	4.12 (0.752)	1.34 (1.032)	3.48 (0.944)
95% CI	(0.34, 3.50)	(2.65, 5.60)	(-0.69, 3.37)	(1.63, 5.33)
Treatment comparison vs. placebo				
LS mean (SE)		**2.21** (0.617)		**2.14** (0.676)
95% CI		(0.99, 3.42)		(0.81, 3.47)
P-value		0.0004		0.0016

Least-squares means, SEs, CIs, and p-values were from a mixed-effects pattern-mixture model with arm, week, ECOG status, BMI group, age group, gender, weight loss over prior 6 months, geographic region group, chemotherapy or radiation therapy status, baseline score, week × arm, death, other, death × week, other × week, death × arm, other × arm, death × arm × week, and other × arm ×

week as fixed effects and random effects of intercept and week, where death = dropout due to death and other = dropout due to other reasons.

1. Number of patients with values at both baseline and post-baseline.

2. Baseline was defined as the last value obtained prior to the first dose of study drug.

Change in SEA (simplified evaluation for appetite; newly developed) score from baseline over 12 weeks

Table 19. Change in SEA score from baseline over 12 weeks - MITT population in Studies HT-ANAM-301 and HT-ANAM-302

time point statistic	ROMANA 1		ROMANA 2	
	placebo N = 141	**anamorelin N = 284**	**placebo N = 136**	**anamorelin N = 268**
Overall				
N [1]	140	281	133	266
change from baseline				
LS mean (SE)	0.92 (0.339)	1.57 (0.317)	0.41 (0.435)	1.08 (0.400)
95% CI	(0.26, 1.59)	(0.95, 2.20)	(-0.44, 1.27)	(0.29, 1.86)
Treatment comparison vs. placebo				
LS mean (SE)		**0.65** (0.262)		**0.66** (0.283)
95% CI		(0.14, 1.16)		(0.11, 1.22)
P-value		0.0134		0.0192

Least-squares means, SEs, CIs, and p-values were from a mixed-effects pattern-mixture model with arm, week, ECOG status, BMI group, age group, gender, weight loss over prior 6 months, geographic region group, chemotherapy or radiation therapy status, baseline score, week × arm, death, other, death × week, other × week, death × arm, other × arm, death × arm × week, and other × arm × week as fixed effects and random effects of intercept and week, where death = dropout due to death and other = dropout due to other reasons.

1. Number of patients with values at both baseline and post-baseline.

2. Baseline was defined as the last value obtained prior to the first dose of study drug.

Change in fatigue domain of the FACIT-F form baseline over 12 weeks (including comment to all other FACIT-F (sub)scores)

Table 20. Change in fatigue domain of FACIT-F from baseline over 12 weeks MITT population in Studies HT-ANAM-301 and HT-ANAM-302

time point statistic	ROMANA 1		ROMANA 2	
	Placebo N = 141	**Anamorelin N = 284**	**Placebo N = 136**	**Anamorelin N = 268**
Overall				
N [1]	140	280	131	265
change from baseline				
LS mean (SE)	-1.19 (0.933)	0.26 (0.886)	1.23 (1.293)	1.37 (1.169)
95% CI	(-3.02, 0.64)	(-1.48, 0.752)	(-1.31, 3.76)	(-0.92, 3.66)
Treatment comparison vs. placebo				
LS mean (SE)		**1.45** (0.752)		**0.14** (0.841)
95% CI		(-0.03, 2.92)		(-1.51, 1.80)
P-value		0.0544		0.8637

Least-squares means, SEs, CIs, and p-values were from a mixed-effects pattern-mixture model with arm, week, ECOG status, BMI group, age group, gender, weight loss over prior 6 months, geographic region group, chemotherapy or radiation therapy status, baseline score, week × arm, death, other, death × week, other × week, death × arm, other × arm, death × arm × week, and other × arm × week as fixed effects and random effects of intercept and week, where death = dropout due to death and other = dropout due to other reasons.

1. Number of patients with values at both baseline and post-baseline.

2. Baseline was defined as the last value obtained prior to the first dose of study drug.

Change in SEF (simplified evaluation for fatigue) score from baseline over 12 weeks

Table 21 . Change in SEF score from baseline over 12 weeks-MITT population in Studies HT-ANAM-301 and HT-ANAM-302

	ROMANA 1		ROMANA 2	
time point statistic	**Placebo N = 141**	**Anamorelin N = 284**	**Placebo N = 136**	**Anamorelin N = 268**
Overall				
N [1]	139	280	131	264
change from baseline				
LS mean (SE)	-023 (0.325)	0.11 (0.309)	0.54 (0.439)	0.53 (0.397)
95% CI	(-086, 0.41)	(-0.50, 0.71)	(-0.32, 1.41)	(-0.25, 1.31)
Treatment comparison vs. placebo				
LS mean (SE)		**0.33** (0.265)		-0.01 (0.287)
95% CI		(-0.19, 0.85)		(-0.58, 0.55)
P-value		0.2098		0.9657

Least-squares means, SEs, CIs, and p-values were from a mixed-effects pattern-mixture model with arm, week, ECOG status, BMI group, age group, gender, weight loss over prior 6 months, geographic region group, chemotherapy or radiation therapy status, baseline score, week × arm, death, other, death × week, other × week, death × arm, other × arm, death × arm × week, and other × arm × week as fixed effects and random effects of intercept and week, where death = dropout due to death and other = dropout due to other reasons.

1. Number of patients with values at both baseline and post-baseline.

2. Baseline was defined as the last value obtained prior to the first dose of study drug.

Other secondary endpoints (selection)

Change in FAACT TOI from baseline over 12 weeks

The treatment comparison between placebo and anamorelin with regard to 'change in FAACT TOI from baseline over 12 weeks' was statistically significant in ROMANA 1 and not statistically significant in ROMANA 2.

Change in FAACT total score from baseline over 12 weeks

The treatment comparison between placebo and anamorelin was not statistically significant with regard to 'change in FAACT total score from baseline over 12 weeks'. While in ROMANA 1 the anamorelin treatment effect still remains mainly stable from week 3 to 12 compared with placebo (the curves open), in ROMANA 2 the anamorelin treatment effect decreases between week 3 to 12 compared with placebo (the curves go parallel). For ROMANA 1 and ROMANA 2 the anamorelin and notably also placebo treatment effect can be seen between baseline and week 3.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trials HT-ANAM-301 and 302 (ROMANA 1 and 2)

Title: Anamorelin HCl in the Treatment of Non-Small Cell Lung Cancer – Cachexia (NSCLC-C): A randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Safety and Efficacy of Anamorelin HCl in Patients with NSCLC-C			
Study identifier	HT-ANAM-301 (ROMANA 1) and HT-ANAM-302 (ROMANA 2)		
Design	phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	08 July 2011 – 28 Jan 2014 (ROMANA 1) 14 July 2011 – 31 Oct 2013 (ROMANA 2) not applicable not applicable (see ROMANA 3)	
Hypothesis	Superiority		
Treatments groups	Anamorelin	Anamorelin 100mg orally QD (1h before the first meal of the day) for 12 weeks (323 patients)	
	Placebo	Placebo orally QD (1h before the first meal of the day) for 12 weeks (161 patients)	
Endpoints and definitions	Co-Primary endpoint	• Change in LBM from baseline as measured by DEXA over 12 weeks, and • Change in HGS of the non-dominant hand from baseline over 12 weeks [change from baseline "over 12 weeks" was defined as the average of the change from baseline at week 6 and change from baseline at week 12]	
	Key secondary endpoints (key secondary endpoints were prespecified in the SAP, but no type I error control or hierarchical testing was performed)	• QoL as assessed by the change from baseline over 12 weeks for the following scores: - A/CS domain of the FAACT, - SEA (subscore within the A/CS domain of the FAACT) - fatigue domain of the FACIT-F, - SEF (subscore within the FACIT-F) [change from baseline "over 12 weeks" was defined as the mean change of the QoL scores from baseline to weeks 3, 6, 9 and 12 estimated using pattern-mixture models] • OS pooled for studies HT-ANAM-301 and HT-ANAM-302	
	Other secondary endpoints (selection)	• QoL as assessed by the change from baseline over 12 weeks for the following scores: - FAACT TOI - FACIT-F TOI - FAACT total score - FACIT-F total score [change from baseline "over 12 weeks" was defined as the mean change of the QoL scores from baseline to weeks 3, 6, 9 and 12 estimated using pattern-mixture models] • OS during 12-month follow-up period in this study • Changes in body weight from baseline to weeks 3, 6, 9 and 12	
Database lock	• excluding survival data: first lock 19 Mar 2014, unlocked/relocked once, final lock 04 Dec 2014 • survival data: 04 Dec 2014		

Results and Analysis (ROMANA 1)

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT		
Descriptive statistics and estimate variability	Treatment group	Placebo	Anamorelin
	Number of subjects	158	316
	Change in **LBM** [median, kg]	-0.47	0.99
	95% CI	-1.00; 0.21	0.61; 1.36
	Change in **HGS** (non-dominant hand) [median, kg]	-1.58	-1.10
	95% CI	-2.99; -1.14	-1.69; -0.40

Effect estimate per comparison	Co-Primary endpoint:	Comparison groups	Anamorelin vs. placebo
	Change in **LBM**	Difference in medians [kg]	1.46
	AND	P-value	< 0.0001
	Change in **HGS** (non-dominant hand)	Difference in medians [kg]	0.48
		P-value	0.1475 (not significant)

Notes	The Co-primary endpoint failed for study HT-ANAM-301 (ROMANA 1).

Analysis description	**Secondary Analysis**
Analysis population and time point description	ITT for OS MITT for all QoL scores

Descriptive statistics and estimate variability	Treatment group	Placebo	Anamorelin
	Number of subjects	326	653
	OS **pooled** for studies HT-ANAM-301 and HT-ANAM-302 [median; months]	9.17	8.90
	95% CI	7.93; 11.00	8.27; 9.80
	Number of subjects	141	282
	QoL: Change in **A/CS** domain of the FAACT [LS mean (SE)]	1.92 (0.805)	4.12 (0.752)
	95% CI	0.34; 3.50	2.65; 5.60
	Number of subjects	140	281
	QoL: Change in **SEA** [LS mean (SE)]	0.92 (0.339)	1.57 (0.317)
	95% CI	0.26; 1.59	0.95; 2.20
	Number of subjects	140	280
	QoL: Change in **fatigue domain** of the FACIT-F [LS mean (SE)]	-1.19 (0.933)	0.26 (0.886)
	95% CI	-3.02; 0.64	-1.48; 0.752
	Number of subjects	139	280
	QoL: Change in **SEF** [LS mean (SE)]	-0.23 (0.325)	0.11 (0.309)
	95% CI	-0.86; 0.41	-0.50; 0.71
	Number of subjects	140	280

	QoL: Change in **FAACT TOI** [LS mean (SE)]	1.91 (1.448)	4.77 (1.341)
	95% CI	-0.93; 4.76	2.14; 7.41
	Number of subjects	140	278
	QoL: Change in **FACIT-F TOI** [LS mean (SE)]	-1.54 (1.652)	0.36 (1.560)
	95% CI	-4.78; 1.70	-2.70; 3.42
	Number of subjects	139	276
	QoL: Change in **FAACT total score** [LS mean (SE)]	3.78 (1.804)	6.46 (1.678)
	95% CI	0.24; 7.32	3.16; 9.75
	Number of subjects	139	275
	QoL: Change in **FACIT-F total score** [LS mean (SE)]	-0.05 (1.998)	2.02 (1.890)
	95% CI	-3.97; 3.88	-1.69; 5.73
	Number of subjects	161	323
	OS study HT-ANAM-301 [median; months]	8.90	8.70
	95% CI	7.70; 10.30	7.60; 10.23

Effect estimate per comparison	Secondary endpoint	Comparison groups	Anamorelin vs. placebo
	OS pooled for studies HT-ANAM-301 and -302	Hazard ratio	1.06
		95% CI	0.89; 1.26
		P-value	0.4691
	QoL: Change in in **A/CS** domain of the FAACT	LS mean (SE)	2.21 (0.617)
		95% CI	(0.99, 3.42)
		P-value	0.0004
	QoL: **SEA**	LS mean (SE)	0.65 (0.262)
		95% CI	0.14, 1.16
		P-value	0.0134
	QoL: Change in **fatigue domain** of the FACIT-F	LS mean (SE)	1.45 (0.752)
		95% CI	-0.03; 2.92
		P-value	0.0544
	QoL: Change in **SEF**	LS mean (SE)	0.33 (0.265)
		95% CI	-0.19; 0.85
		P-value	0.2098
	QoL: Change in **FAACT TOI**	LS mean (SE)	2.86 (1.161)
		95% CI	0.58, 5.14)
		P-value	0.0140
	QoL: Change in **FACIT-F TOI**	LS mean (SE)	1.90 (1.358)
		95% CI	-0.77; 4.56
		P-value	0.1624
	QoL: Change in **FAACT total score**	LS mean (SE)	2.67 (1.459)
		95% CI	-0.19; 5.54
		P-value	0.0673
	QoL: Change in **FACIT-F total score**	LS mean (SE)	2.07 (1.651)
		95% CI	-1.17; 5.31
		P-value	0.2110
	OS study HT-ANAM-301	Hazard ratio	0.96
		95% CI	0.76; 1.23
		P-value	0.7290

Notes	The applicant has prespecified in the SAP 5 so-called key secondary endpoints without performing type I error control and/or hierarchical testing. Minimally important difference (MID) as a threshold to define a clinically relevant difference in the scores for each used QoL questionnaire was not defined prospectively in the study protocol or SAP but is only discussed retrospectively in the CSR.

Results and Analysis (ROMANA 2)

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT		
Descriptive statistics and estimate variability	Treatment group	Placebo	Anamorelin
	Number of subjects	157	321
	Change in **LBM** [median, kg]	-0.98	0.65
	95% CI	-1.49; -0.41	0.38; 0.91
	Change in **HGS** (non-dominant hand) [median, kg]	-0.95	-1.49
	95% CI	-1.56, 0.04	-2.06, -0.58

Effect estimate per comparison	Co-Primary endpoint:	Comparison groups	Anamorelin vs. placebo
	Change in **LBM**	Difference in medians [kg]	1.63
	AND	P-value	< 0.0001
	Change in **HGS** (non-dominant hand)	Difference in medians [kg]	-0.53
		P-value	0.6480

Notes	The Co-primary endpoint failed for study HT-ANAM-302 (ROMANA 2).

Analysis description	**Secondary Analysis**		
Analysis population and time point description	ITT for OS MITT for all QoL scores		
Descriptive statistics and estimate variability	Treatment group	Placebo	Anamorelin
	Number of subjects	326	653
	OS pooled for studies HT-ANAM-301 and HT-ANAM-302 [median; months]	9.17	8.90
	95% CI	7.93; 11.00	8.27; 9.80
	Number of subjects	133	266
	QoL: Change in **A/CS** domain of the FAACT [LS mean (SE)]	1.34 (1.032)	3.48 (0.944)
	95% CI	-0.69; 3.37	1.63; 5.33
	Number of subjects	133	266
	QoL: Change in **SEA** [LS mean (SE)]	0.41 (0.435)	1.08 (0.400)
	95% CI	-0.44; 1.27	0.29; 1.86
	Number of subjects	131	265

	QoL: Change in **fatigue domain** of the FACIT-F [LS mean (SE)]	1.23 (1.293)	1.37 (1.169)
	95% CI	-1.31; 3.76	-0.92; 3.66
	Number of subjects	131	264
	QoL: Change in **SEF** [LS mean (SE)]	0.54 (0.439)	0.53 (0.397)
	95% CI	-0.32; 1.41	-0.25; 1.31
	Number of subjects	132	264
	QoL: Change in **FAACT TOI** [LS mean (SE)]	3.29 (1.910)	5.05 (1.728)
	95% CI	-0.46; 7.04	1.66; 8.44
	Number of subjects	131	263
	QoL: Change in **FACIT-F TOI** [LS mean (SE)]	2.82 (2.195)	2.61 (1.978)
	95% CI	-1.49; 7.13	-1.28; 6.49
	Number of subjects	132	264
	QoL: Change in **FAACT total score** [LS mean (SE)]	4.66 (2.442)	6.07 (2.204)
	95% CI	-0.13; 9.46	1.74; 10.40
	Number of subjects	131	263
	QoL: Change in **FACIT-F total score** [LS mean (SE)]	3.73 (2.712)	3.17 (2.441)
	95% CI	-1.60; 9.05	-1.62; 7.97
	Number of subjects	165	330
	OS study HT-ANAM-302 [median; months]	10.30	9.03
	95% CI	7.67; NE	8.00; 10.23

Effect estimate per comparison	Secondary endpoint	Comparison groups	Anamorelin vs. placebo
	OS pooled for studies HT-ANAM-301 and -302	Hazard ratio	1.06
		95% CI	0.89; 1.26
		P-value	0.4691
	QoL: Change in in **A/CS** domain of the FAACT	LS mean (SE)	2.14 (0.676)
		95% CI	0.81; 3.47
		P-value	0.0016
	QoL: Change in **SEA**	LS mean (SE)	0.66 (0.283)
		95% CI	0.11; 1.22
		P-value	0.0192
	QoL: Change in **fatigue domain** of the FACIT-F	LS mean (SE)	0.14 (0.841)
		95% CI	-1.51; 1.80
		P-value	0.8637
	QoL: Change in **SEF**	LS mean (SE)	-0.01 (0.287)
		95% CI	-0.58; 0.55
		P-value	0.9657
	QoL: Change in **FAACT TOI**	LS mean (SE)	1.76 (1.274)
		95% CI	-0.74; 4.26
		P-value	0.1674
	QoL: Change in **FACIT-F TOI**	LS mean (SE)	-0.21 (1.454)
		95% CI	-3.07; 2.65

		P-value	0.8852
	QoL: Change in **FAACT total score**	LS mean (SE)	1.40 (1.634)
		95% CI	-1.80; 4.61
		P-value	0.3901
	QoL: Change in **FACIT-F total score**	LS mean (SE)	-0.56 (1.804)
		95% CI	-4.10; 2.99
		P-value	0.7583
	OS study HT-ANAM-302	Hazard ratio	1.19
		95% CI	0.93; 1.53
		P-value	0.1698
Notes	The applicant has prespecified in the SAP 5 so-called key secondary endpoints without performing type I error control and/or hierarchical testing. Minimally important difference (MID) as a threshold to define a clinically relevant difference in the scores for each used QoL questionnaire was not defined prospectively in the study protocol or SAP but is only discussed retrospectively in the CSR.		

Analysis performed across trials (pooled analyses and meta-analysis)

A series of additional analyses were conducted, aimed at exploring the actual clinical benefit attainable with anamorelin administration to subjects with Non-small cell lung cancer cachexia (NSCLC-C); these analyses are deemed complementary to the primary, secondary and exploratory analyses conducted per original protocols and statistical analysis plan.

The analyses were based on pooled data from the two identical multinational randomized double-blind placebo-controlled studies HT-ANAM-301 and HT-ANAM-302. Different from the original analyses, missing data were imputed for all parameters by last-observation-carried-forward (LOCF) method from Week 6 onward. Analyses at Week 12 with LOCF were defined as End of Study (EOS), as in fact the last available value on study was used.

Table 22. Pooled analysis of changes from baseline and responders' analysis for lean body mass in Studies HT-ANAM-301 and HT-ANAM-302

	All Subjects	BMI < 20 kg/m^2	Weight loss ≥10%	FAACT A/CS≤30	CRP > 10mg/L
Placebo					
N	256	64	106	114	168
Matching Baseline, mean (SD)	45.12 (8.61)	39.54 (6.79)	42.40 (8.42)	43.04 (7.72)	45.85 (8.03)
Change from Baseline, mean (SD)	-0.37 (2.69)	-0.46 (2.59)	-0.45 (2.80)	-0.51 (2.72)	-0.60 (2.85)
Anamorelin					
N	520	103	206	252	320
Matching Baseline, mean (SD)	45.50 (7.97)	40.13 (6.67)	43.41 (7.75)	43.76 (8.02)	45.67 (7.98)
Change from Baseline, mean (SD)	1.16 (2.71)	1.25 (2.66)	1.33 (2.82)	1.01 (2.71)	0.95 (2.78)
Treatment difference					
Point Estimate (95% CI)	1.52 (1.12, 1.93)	1.71 (0.88, 2.54)	1.78 (1.12, 2.44)	1.52 (0.92, 2.12)	1.55 (1.02, 2.07)
p value	<.001	<.001	<.001	<.001	<.001
Standardized effect size					
Point Estimate (95% CI)	0.57 (0.42, 0.72)	0.80 (0.48, 1.11)	0.75 (0.52, 0.99)	0.66 (0.44, 0.88)	0.56 (0.37, 0.74)
Response					
Placebo n (%)	75 (29.3)	14 (21.9)	29 (27.4)	30 (26.3)	47 (28)
Anamorelin n (%)	276 (53.1)	59 (57.3)	114 (55.3)	133 (52.8)	155 (48.4)
Ratio Point Estimate (95% CI)	1.80 (1.46, 2.21)	2.69 (1.66, 4.34)	2.02 (1.46, 2.81)	2.00 (1.44, 2.77)	1.73 (1.33, 2.26)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001
NNT	4.2	2.8	3.6	3.8	4.9

Post-hoc sub-group analysis

Further to the initial submission and in order to support an amended indication for the treatment of anorexia, cachexia or unintended weight loss in adult patients with non-small cell lung cancer (NSCLC) and Body Mass Index (BMI) < 20 kg/m^2 the applicant submitted a post-hoc sub-group analysis for various endpoints based on patients BMI. The results from this analysis are presented in **Tables 23-25**.

Table 23. Changes from Baseline to End of Study in Body Composition parameters overall and by BMI inclusion criterion– mITT Set Pooled HT-ANAM-301 and HT-ANAM-302

	Placebo			Anamorelin			Difference		
	N	Matching Baseline	Change From Baseline	N	Matching Baseline	Change From Baseline	Point Estimate	95% CI	Nominal p-value
Total Body Mass									
All patients	256	65.95 (13.71)	-0.71 (4.01)	520	66.98 (13.13)	1.79 (4.55)	2.5 (4.38)	1.84, 3.16	<.001
BMI < 20 kg/m²	**64**	**51.95 (8.28)**	**-0.93 (3.19)**	**103**	**52.02 (7.05)**	**2.44 (4.77)**	**3.37 (4.24)**	**2.04, 4.70**	**<.001**
BMI ≥ 20 kg/m²	192	70.62 (11.87)	-0.64 (4.26)	417	70.68 (11.57)	1.63 (4.49)	2.26 (4.42)	1.51, 3.02	<.001
Total Lean Mass									
All patients	256	45.12 (8.61)	-0.37 (2.69)	520	45.5 (7.97)	1.16 (2.71)	1.52 (2.71)	1.12, 1.93	<.001
BMI < 20 kg/m²	**64**	**39.54 (6.79)**	**-0.46 (2.59)**	**103**	**40.13 (6.67)**	**1.25 (2.66)**	**1.71 (2.64)**	**0.88, 2.54**	**<.001**
BMI ≥ 20 kg/m²	192	46.98 (8.36)	-0.34 (2.73)	417	46.83 (7.71)	1.13 (2.73)	1.47 (2.73)	1.00, 1.94	<.001

Table 24. Changes from Baseline in FAACT A/CS and FACIT-F Fatigue domain scores in patients with low and high BMI at baseline –EOS

	Placebo			Anamorelin			Difference		
	N	Matching Baseline	Change From Baseline	N	Matching Baseline	Change From Baseline	Point Estimate	95% CI	p-value
FAACT A/CS Domain Score									
All patients	270	30.02 (8.46)	1.59 (9.11)	539	29.6 (8.3)	3.43 (9.15)	1.84 (9.14)	0.50, 3.18	0.007
BMI < 20 kg/m²	**64**	**27.77 (8.02)**	**0.45 (10.46)**	**109**	**25.48 (8.39)**	**5.73 (9.99)**	**5.27 (10.16)**	**2.11, 8.43**	**0.001**
BMI ≥ 20 kg/m²	206	30.71 (8.48)	1.95 (8.65)	430	30.64 (7.96)	2.85 (8.85)	0.91 (8.79)	-0.56, 2.37	0.224
FACIT-F Fatigue Domain Score									
All patients	267	30.74 (10.65)	-0.91 (10.39)	535	30.46 (10.39)	-0.35 (9.93)	0.56 (10.09)	-0.92, 2.05	0.455
BMI < 20 kg/m²	**63**	**30.25 (11.06)**	**-3.22 (10.62)**	**109**	**27.74 (11.69)**	**0.72 (10.94)**	**3.94 (10.82)**	**0.56, 7.32**	**0.023**
BMI ≥ 20 kg/m²	204	30.89 (10.55)	-0.2 (10.24)	426	31.15 (9.93)	-0.62 (9.66)	-0.42 (9.85)	-2.07, 1.23	0.616

Table 25. Responder analysis for Body Composition and Quality of Life parameters in patients with low and high baseline BMI at week 12

	Placebo (N = 277) Absolute values	%	Anamorelin (N= 552) Absolute values	%	Ratio	(95% CI)
Total Mass; increase by 0.5 kg at 6, or by 1.0kg at week 12						
All Subjects	82/256	32.0%	300/520	57.7%	1.79	(1.48, 2.17)
BMI < 20 kg/m²	**20/ 64**	**31.3%**	**64/103**	**62.1%**	**2.00**	**(1.35, 2.94)**
BMI ≥ 20 kg/m²	62/192	32.3%	236/417	56.6%	1.74	(1.40, 2.18)
Total Lean Mass; increase by 0.5 kg at 6, or by 1.0kg at week 12						
All Subjects	75/256	29.3%	276/520	53.1%	1.80	(1.46, 2.21)
BMI < 20 kg/m²	**14/ 64**	**21.9%**	**59/103**	**57.3%**	**2.69**	**(1.66, 4.34)**
BMI ≥ 20 kg/m²	61/192	31.8%	217/417	52.0%	1.64	(1.30, 2.05)
Appendicular LBM; increase by 0.5 kg at 6, or by 1.0kg at week 12						
All Subjects	51/256	19.9%	196/520	37.7%	1.90	(1.45, 2.48)
BMI < 20 kg/m²	**10/64**	**15.6%**	**43/103**	**41.7%**	**2.74**	**(1.51, 4.97)**
BMI ≥ 20 kg/m²	41/192	21.4%	153/417	36.7%	1.75	(1.30, 2.35)
Total Fat Mass; increase by 0.25kg at 6, or by 0.5kg at week 12						
All Subjects	90/256	35.2%	275/520	52.9%	1.49	(1.24, 1.79)
BMI < 20 kg/m²	**19/ 64**	**29.7%**	**58/103**	**56.3%**	**1.87**	**(1.24, 2.83)**
BMI ≥ 20 kg/m²	71/192	37.0%	217/417	52.0%	1.40	(1.14, 1.72)
FAACT A/CS Domain Score; increase by 4						
All Subjects	101/270	37.4%	271/539	50.3%	1.35	(1.13, 1.61)
BMI < 20 kg/m²	**22/ 64**	**34.4%**	**64/109**	**58.7%**	**1.65**	**(1.13, 2.40)**
BMI ≥ 20 kg/m²	79/206	38.3%	207/430	48.1%	1.26	(1.03, 1.53)
FACIT-F Fatigue Domain Score; increase by 4						
All Subjects	80/267	30.0%	170/535	31.8%	1.05	(0.85, 1.31)
BMI < 20 kg/m²	**15/ 63**	**23.8%**	**36/109**	**33.0%**	**1.29**	**(0.76, 2.17)**
BMI ≥ 20 kg/m²	65/204	31.9%	134/426	31.5%	0.98	(0.77, 1.25)

Clinical studies in special populations

The applicant did not submit any studies in special popualtions.

Supportive study

Study 303: HT-ANAM-303 (ROMANA 3) Anamorelin HCl in the Treatment of Non-Small Cell Lung Cancer-Cachexia (NSCLC-C): A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Phase 3 Extension Study to Evaluate the Safety and Efficacy of Anamorelin HCl in Subjects with NSCLC-C.

The study was a randomized, double-blind, parallel-group, placebo-controlled, extension study to assess the safety and efficacy of anamorelin HCl in NSCLC-C subjects. Subjects who completed dosing in either of the original studies of anamorelin HC1 in the treatment of NSCLC-C (HT-ANAM-301 or HT-ANAM-302), were able to enroll in this study and continue to receive the study drug to which they were assigned, either anamorelin HC1 100 mg or placebo once daily (QD) for an additional 12 weeks. Subjects were instructed to take the study drug at least 1 hour before their first meal of the day.

The study was approximately 17 weeks in duration, including a screening period of up to 1 week, a 12-week treatment period, and a 4-week follow-up period.

The results showed sustained weight gain in both active and placebo groups, with a statistically significant difference of 2.13kg over placebo for anamorelin. No differences were again seen in handgrip strength and most of the QoL measures showed no overall differences.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Three Phase 2 studies were submitted to support the hypothesis that anamorelin represents a potential treatment of anorexia-cachexia in subjects with advanced solid malignancies, including NSCLC.

The efficacy of anamorelin in subjects with advanced NSCLC and cachexia has been evaluated in two Phase 3 studies, followed by a 12-week safety extension study. The two pivotal phase 3 studies were identical in design and methods with regard to efficacy and safety.

The efficacy part of the development programme was adequately designed. The phase II proof of concept and dose ranging studies were adequately conducted.

However, the interpretation of the results and the use of endpoints from these in the phase III studies are questioned. The decision to use hand grip strength as a co-primary in the phase III studies was not intuitive when the endpoint was seen to fail in two out of the three phase II studies.

Scientific advice was given by CHMP concerning clinical efficacy in the phase 3 study program in January 2012 (EMA/CHMP/SAWP/9760/2012). The co-primary endpoint [‘change in lean body mass’ (LBM) and ‘change in handgrip strength’ (HGS)] was criticised as in a population with very limited life expectancy improvements in quality of life (QoL) were considered as more informative and clinically meaningful than muscle mass assessment. Demonstration of a clear effect on one objective variable reliably measuring anabolic drug activity combined with one adequately validated subjective/functional variable ensuring patient relevance was considered the preferred option. Advice was not adopted by the Applicant as the two pivotal studies were already ongoing for around 6 months while seeking scientific advice.

In the pivotal trials 8 QoL instruments were tested as secondary endpoints, 4 (total score, TOI, A/CS and SEA) belonging to the FAACT instrument and 4 (total score, TOI, fatigue domain, SEF) belonging to the FACTI-F instrument. For interpretation of the the QoL results it needs to be taken into consideration that SEA is a sub-score of A/CS, which is a sub-score of FAACT TOI, which is a sub-score of FAACT total score. The same applies to FACIT-F scores tested. SEA and SEF score were developed and validated by the applicant within the pivotal trials and have to be seen as questionable for interpretation of the pivotal trial results. No minimally important differences (MID) were pre-specified to define thresholds identifying clinically significant changes.

Importantly even though 8 QoL instruments were tested as secondary endpoints, no hierarchy and no type I error control was established to control for multiple testing. Furthermore the pre-specified method for analysis aims at estimation of the treatment effect that would have been observed if all patients had survived until week 12 and all patients had been fully adherent to treatment. This is likely to overestimate any treatment effect that would be observed in clinical practice.

Efficacy data and additional analyses

Phase 2 studies

The results of study 203/205 showed the expected rise in the biomarkers that would be relevant to a ghrelin agonist. Changes in overall body mass, lean body mass and weight were all seen and correlated well together, indicating an increase in muscle mass rather than fat or fluid. Handgrip strength also increased over baseline when compared to placebo in a statistically significant manner.

However, he QoL measures were not significant at week 12. Overall, the study could be seen as a successful proof of concept with regards biomarkers for mechanism of action and increases in lean body mass and weight.

Study 206 looked at two doses of anamorelin, 50mg and 100mg QD. Increases in body weight were seen in both active treatment arms over 4 weeks, with the change being greater with 50mg that 100mg. Moreover, the 50mg was statistically superior to placebo at week 4 but 100mg was not. Between weeks 4-12, subjects that continued on 50mg lost weight (-0.73 kg); not a small weight loss as posed by the applicant. Those that continued on 100mg gained weight, as did those that switched from placebo to 100mg. Handgrip strength failed to show any significant changes from baseline for either active treatment, although both active groups did not decline from baseline, whereas placebo did. In conclusion, the results across study 206 were more inconsistent than with 203/205.

Study 207 again compared 50mg, 100mg and placebo, this time over a 12 week period. The selection of the dose for the subsequent phase III studies was made based on the results of this study. However, as the study failed, being statistically superior only to placebo on one of the two co-primary endpoints, makes it difficult to interpret the rest of the data and confirm that the dose selection was correct.

Looking at the mean change from baseline for bodyweight with the 100mg dose, it can be seen that bodyweight whilst maintained, did not show any significant increase. This was reflected in the 50mg dose as well, whilst those on placebo lost bodyweight over the course of the study.

Other endpoints such as tumour progression and survival showed no statistical difference which is not unexpected given the mechanism of action. Of concern however is the trend in the survival data for active to be worse than placebo, which is discussed further in the safety section.

Whilst pharmacodynamic responses have been seen across the three phase II studies and for both investigated doses, this has not been translated into a consistent set of results across the clinical efficacy endpoints. In addition, the two trials that compared 50mg and 100mg had inconsistent results. Body weight increased more in the 50mg group in study 206 and in 207 no significant changes from baseline were observed. Further to this there was no correlation in these studies with handgrip strength or QoL measures; it is therefore difficult to see what benefits the anamorelin conferred on subjects in these studies or the rationale for selecting the 100mg preferentially over the 50 mg dose.

Phase 3 studies

In the the pivotal trials 301 and 302 were based upon the results from the phase II studies, particularly 207 and the dose ranging that the applicant performed in that study. There is significant uncertainty within the dose selection and the use of the phase II studies endpoints given the results obtained. The dose selection is discussed above.

The endpoints selected for the pivotal trials 301 and 302, with the exception of body mass, had performed inconsistently across the phase II studies. The choice of handgrip strength as a co-primary was not intuitive when looking at the fact that the endpoint failed in the two out of three phase II studies and in the one that was conducted in this population and with this dose (207). The applicant has also had difficulty in finding a QoL measure that is relevant and positive in phase II and with the introduction of a new measure untested with the active and indication before, the impact on the clinical assessment was limited. The demographics and baseline characteristics of the subjects were acceptable. However, in both studies mean BMI of the ITT population was in the normal range (23.30 and 22.39 kg/m^2 respectively), although dealing with an anorectic/cachectic study population.

Furthermore in the view of the long time since the primary tumour diagnosis it appears surprising that >50% patients were included with no previous antitumor treatment.

With regard to statistics there were some issues with the analysis populations used and the exclusion of some subjects. The methods of analysis and the handling of missing data hindered the interpretation of the results. .

Co-primary endpoints

The results of the co-primaries raised significant issues with regards to the efficacy of anamorelin in the indication requested. Whilst a statistically significant difference in favour of the active over placebo was found for lean body mass, the difference was not as large as anticipated; only 1.46 kg and 1.63 kg respectively compared to the 2 kg used in the sample size calculation. The median change from baseline was 0.99 kg and 0.65 kg respectively weight gain for anamorelin. Given this, the clinical meaning of this result in isolation is not clear and is even less clear when considering the overall results of the trial.

The handgrip strength co-primary failed in both pivotal trials, with no statistical difference between active and placebo. This renders the studies a failure and means that the secondary endpoints should formally not have been assessed. The CHMP also noted that this endpoint had failed to detect any meaningful differences in previously conducted studies. Moreover, CHMP's recommendation for a well-established QoL-Co-primary endpoint was not followed.

Quality of life (QoL) endpoints

Of note for all QoL endpoints is that information on completeness / missing data imputation was not found in the dossier. Therefore the interpretation of the QoL data needs to be cautious.

Overall, the QoL endpoints in both pivotal trials give a negative picture. All but A/CS and the newly developed SEA (an A/CS sub-score) did not achieve statistical significance in both pivotal trials. And none of all QoL endpoints tested achieved the clinically meaningful changes according to the literature-based MIDs.

The pre-specified method of analysis aimed at estimation of the treatment effect that would have been observed if all patients had survived until week 12 and all patients had been fully adherent to treatment. When sensitivity analyses were presented under more relevant assumptions, the treatment effects became smaller and of even more questionable clinical significance.

The other secondary and exploratory endpoints also do not support a clinically meaningful change to subject's QoL.

Therefore, given the results of the pivotal studies and the failure of a co-primary endpoint, it is difficult to see any clinically compelling argument of efficacy and benefit.

Extension study

With the caveats discussed above in the pivotal trials, the extension trial was adequately designed and conducted. The results of this study showed sustained weight gain in both active and placebo groups, with a statistically significant difference of 2.13 kg over placebo for anamorelin. This was the only study for which such a significant change was reported. However, the CHMP noted that as this was an an extension study, the population has self-selected to an extent. This means that only those whom have had either the most efficacy or were most motivated had continued. This was reflected by the fact that the placebo group has also gained nearly 1kg of weight over the extension study. No differences were again seen in handgrip strength and most of the QoL measures showed no overall

differences. Again, those that did (A/CS domain of FAACT and SEA) did not show clinically meaningful increases as set out in the applicant's pivotal studies. The efficacy part of the extension trial can therefore be seen to further reflect the minimal efficacy of the pivotal trials continuing over time.

The pooled data and its additional analyses also reflect the results seen across the studies and add little to the efficacy picture. During the assessment procedure the applicant suggested changing the indication to only patients with BMI < 20 Kg/m^2 based on a post-hoc subgroup analysis of the pooled data. However this was not accepted given the data driven approach to the analysis whereas the pre-specified subgroup analysis by BMI (cut–off 18.5 Kg/m^2) did not support the conclusion of higher efficacy in patients whith lower BMI. Moreover the randomisation was not stratified by BMI and therefore there could be imbalances in the baseline characteristics favouring anamorelin.

Additional expert consultation

In the course of the evaluation procedure, the CHMP identified the need for input from patient representatives. Two patients with lung cancer, one of which had experienced cachexia during the course of his disease, participated in an oral explanation where the applicant addressed the outstanding issues before the CHMP. The patients expressed the view that the observed increase in lean body mass was not meaniglul in the context of the applied indication. Furthermore, they highlighted that the individual positive results in isolated sub-scores for the quality of life measures, could not be considered indicative of truly positive effect of anamorelin.

2.5.4. Conclusions on the clinical efficacy

The results of the studies across the clinical development programme have consistently shown that the selected 100mg dose has modest effects on lean body mass and total body weight, leading to maintenance of baseline values or slight only increases. As stated in the scientific advice given by CHMP, lean body mass has limited clinical significance on its own and an increase in muscle mass and other body mass parameters alone cannot be regarded as clinically meaningful.

Handgrip strength endpoints failed in all but one study (phase II) and therefore both pivotal are considered as negative. In addition, the QoL endpoints have failed to give a significant difference over placebo or have not reached the threshold that is described in literature as a clinically meaningful difference. Moreover, for the clinical trials planned CHMP had recommended inclusion of a well-established and validated QoL co-primary endpoint in order concluding that a clinical relevant increase of LBM has a clinical relevant impact on the patient's QoL. However, this option was not chosen from the applicant.

Therefore, the CHMP concluded that the therapeutic efficacy of anamorelin is not established. Restriction of the indication to patients with a BMI < 20 as proposed by the applicant was also not considered acceptable due to significant statistical violations, most importantly that this subgroup was prioritised post hoc.

2.6. Clinical safety

Patient exposure

The clinical development program for anamorelin HCl for the cancer cachexia indication comprises 12 Phase 1 studies, four Phase 2 studies, and two Phase 3 studies (HT-ANAM-301 and HT-ANAM-302) followed by a 12-week safety double-blind extension study (HT-ANAM-303).

The integrated safety database for anamorelin HCl consists of six pooled Phase 2 and Phase 3 studies (RC-1291-203/205, RC-1291-206, ST-ANAM- 207, HT-ANAM-301, and HT-ANAM-302). This integrated safety database was organized into distinct datasets, according to the nature of the data provided (i.e., study phase and patient population). This breakdown is summarized in **Table 26.**

Table 26. Subjects included in the Integrated Safety Analysis Set A (pivotal phase 3 studies in NSCLC) and Set C (Integrated Phase 2 and 3 Studies in all types of cancer)

	Safety Set				
	Set A		Set C		
Phase Indication	Placebo N = 322	Anamorelin HCl 100 mg N = 650	Placebo N = 437	Anamorelin HCl 50 mg N = 136	Anamorelin HCl 100 mg N = 743
Phase 3					
NSCLC	322	650	322	n/a	650
Phase 2					
NSCLC and other	n/a	n/a	115	136	93

Set A includes studies HT-ANAM-301 and HT-ANAM-302 for NSCLC patients.
Set C includes Studies RC-1291-203/205, RC-1291-206, ST-ANAM-207, HT-ANAM-301, and HT-ANAM-302 for all cancer patients.
n/a = not applicable

A total of 879 patients with various cancers received anamorelin HCl treatment (Set C); 809 patients with NSCLC and 70 patients with other types of cancers. Among the 809 patients, 724 patients received 100 mg and 85 patients received 50 mg anamorelin HCl treatment.

Six hundred fifty (650) patients received anamorelin HCl 100 mg in the randomized Phase 3 studies (Set A) (HT-ANAM-301 and HT-ANAM-302).

The demographic and baseline charactersitics of the safety population is presented in **Table 27**.

Table 27. Demographic and baseline characterstics of the integrated safety population (Sets A and C).

Statistic/Category	Placebo	Anamorelin HCl 50mg	Anamorelin HCl 100mg	Total
	(N=437)	(N=136)	(N=743)	(N=1316)
Age (years) at Screening				
N	437	136	743	1316
Mean (SD)	62.1 (9.75)	60.1 (13.57)	62.2 (9.26)	61.9 (9.96)
Age Group (n, %)				
≤65 years	292 (66.8)	83 (61.0)	485 (65.3)	860 (65.3)
>65 years	145 (33.2)	53 (39.0)	258 (34.7)	456 (34.7)
<75 years	389 (89.0)	118 (86.8)	675 (90.8)	1182 (89.9)
≥75 years	48 (11.0)	18 (13.2)	68 (9.1%)	134 (10.1)
Gender (n, %)				
Male	325 (74.4)	89 (65.4)	559 (75.2)	973 (73.9)
Female	112 (25.6)	47 (34.6)	184 (24.8)	343 (26.1)
Race (n, %)				
White	357 (81.7)	62 (45.6)	664 (89.4)	1083 (82.3)
Black or African American	11 (2.5)	11 (8.1)	9 (1.2)	31 (2.4)
Asian	66 (15.1)	62 (45.6)	66 (8.9)	194 (14.7)
American-Indian or Alaskan Native	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.1)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Other	1 (0.2)	0 (0.0)	1 (0.1)	2 (0.2)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Geographic Region (n, %)				
North America	74 (16.9)	75 (55.1)	74 (10.0)	223 (16.9)
West Europe	136 (31.1)	0 (0.0)	262 (35.3)	398 (30.2)
East Europe + Russia	157 (35.9)	0 (0.0)	330 (44.4)	487 (37.0)
Australia	8 (1.8)	0 (0.0)	14 (1.9)	22 (1.7)
Asia	62 (14.2)	61 (44.9)	63 (8.5)	186 (14.1)
Height (cm)				
N	437	136	743	1316
Mean (SD)	168.6 (9.24)	165.7 (9.81)	168.8 (8.82)	168.4 (9.11)
Weight (kg)				
N	437	136	743	1316
Mean (SD)	63.66 (14.068)	58.44 (13.09)	64.44 (13.618)	63.56 (13.821)
Body Mass Index (kg/m^2)				
N	437	136	743	1316
Mean (SD)	22.28 (3.949)	21.18 (3.922)	22.5 (3.755)	22.29 (3.854)
Body Mass Index Group (n, %)				
≤18.5 kg/m^2	74 (16.9)	37 (27.2)	117 (15.7)	228 (17.3)
>18.5 kg/m^2	363 (83.1)	99 (72.8)	626 (84.3)	1088 (82.7)

Patient disposition status and primary reasons for discontinuation are summarized for each of the Safety Sets in **Table 28**.

Table 28. Patient Disposition and Reasons for Discontinuation – Safety Population – Set A and Set C

	Safety Set				
	Set A		Set C		
	Placebo N = 322 n (%)	Anamorelin HCl 100 mg N = 650 n (%)	Placebo N = 437 n (%)	Anamorelin HCl 50 mg N = 136 n (%)	Anamorelin HCl 100 mg N = 743 n (%)
Patients treated	322 (100.0)	650 (100.0)	437 (100.0)	136 (100.0)	743 (100.0)
Completed treatment [1] [2]	237 (73.6)	471 (72.5)	n/a	n/a	n/a
Completed the study [1]	239 (74.2)	464 (71.4)	313 (71.6)	68 (50.0)	523 (70.4)
Patients discontinued from the study					
Adverse event related to study drug [3]	2 (0.6)	3 (0.5)	13 (3.0)	9 (6.6)	26 (3.5)
Adverse event unrelated to study drug [3]	7 (2.2)	18 (2.8)	n/a	n/a	n/a
Withdrawal by patient	31 (9.6)	64 (9.8)	46 (10.5)	30 (22.1)	76 (10.2)
Protocol violation	0 (0.0)	0 (0.0)	2 (0.5)	2 (1.5)	0 (0.0)
Physician decision [4]	n/a	n/a	4 (0.9)	4 (2.9)	3 (0.4)
Lost to follow-up	1 (0.3)	5 (0.8)	3 (0.7)	3 (2.2)	5 (0.7)
Disease progression [5]	n/a	n/a	1 (0.2)	2 (1.5)	3 (0.4)
Death	34 (10.6)	83 (12.8)	43 (9.8)	13 (9.6)	94 (12.7)
Other	8 (2.5)	13 (2.0)	12 (2.7)	5 (3.7)	13 (1.7)

Set A includes studies HT-ANAM-301 and HT-ANAM-302 for NSCLC patients.
Set C includes Studies RC-1291-203/205, RC-1291-206, ST-ANAM-207, HT-ANAM-301, and HT-ANAM-302 for all cancer patients.
Percentage is calculated using the number of patients in the column heading as the denominator.
1. *Definitions are the same from the individual protocols.*
2. *Set C does not identify how many patients completed treatment.*
3. *Set C does not distinguish between adverse events related or unrelated to study drug. For Sets B and C, "Adverse event related to study drug" represents discontinuation to due to adverse events regardless of relation to study drug.*
4. *Set A did not have "physician decision" as an* as an option for reason for discontinuation.
5. *Set A did not have "disease progression" as an option for reason for discontinuation. n/a = not applicable*

Adverse events

An overview of adverse events reported in Sets A and C are presented in **Table 29**.

Table 29. Overview of Adverse Events in the total Safety Population of the pivotal phase III trials (Safety set A)

Adverse Event Category	**Placebo N = 322 n (%)**	**Anamorelin 100 mg N = 650 n (%)**	**Total N = 972 n (%)**
Any TEAEs [1]	237 (73.6)	**507 (78.0)**	744 (76.5)
Drug-related TEAEs	31 (9.6)	**98 (15.1)**	129 (13.3)
Any chemotherapy-related TEAE	148 (46.0)	**319 (49.1)**	467 (48.0)
TEAE by maximum CTCAE severity [2]			
Any TEAEs			
Grade 3	64 (19.9)	125 (19.2)	189 (19.4)
Grade 4	10 (3.1)	26 (4.0)	36 (3.7)
Grade 5	50 (15.5)	105 (16.2)	155 (15.9)
Drug-related TEAEs			

Grade 3	6 (1.9)	11 (1.7)	17 (1.7)
Grade 4	0 (0.0)	2 (0.3)	2 (0.2)
Grade 5	0 (0.0)	1 (0.2)	1 (0.1)
Deaths [3]	51 (15.8)	107 (16.5)	158 (16.3)
TEAE Leading to Deaths [3]	50 (15.5)	105 (16.2)	155 (15.9)
SAEs			
Any SAEs	88 (27.3)	181 (27.8)	269 (27.7)
Treatment-emergent SAEs	86 (26.7)	178 (27.4)	264 (27.2)
Drug-related treatment-emergent SAEs	0 (0.0)	5 (0.8)	5 (0.5)
Discontinuation of study drug due to AEs			
Any AEs	44 (13.7)	102 (15.7)	146 (15.0)
TEAEs	42 (13.0)	100 (15.4)	142 (14.6)
Drug-related TEAEs	2 (0.6)	5 (0.8)	7 (0.7)

Table 30. Overview of adverse event- Safety population, Set C

Adverse Event Category	**Placebo N = 437 n (%)**	**Anamorelin HCl 50 mg N = 136 n (%)**	**Anamorelin HCl 100 mg N = 743 n (%)**	**Total N = 1316 n (%)**
Any TEAEs [1]	342 (78.3)	128 (94.1)	596 (80.2)	1066
Drug-related TEAEs	46 (10.5)	19 (14.0)	108 (14.5)	173
TEAE by maximum CTCAE severity [2]				
Any TEAEs				
Grade 3	98 (22.4)	45 (33.1)	145 (19.5)	288
Grade 4	17 (3.9)	3 (2.2)	30 (4.0)	50 (3.8)
Grade 5	64 (14.6)	22 (16.2)	122 (16.4)	208 (15.8)
Drug-related TEAEs				
Grade 3	7 (1.6)	6 (4.4)	11 (1.5)	24 (1.8)
Grade 4	0 (0.0)	0 (0.0)	3 (0.4)	3 (0.2)
Grade 5	1 (0.2)	0 (0.0)	2 (0.3)	3 (0.2)
Deaths [3]	66 (15.1)	23 (16.9)	124 (16.7)	213
TEAE Leading to Deaths [3]	64 (14.6)	22 (16.2)	122 (16.4)	208
SAEs				
Any SAEs	128 (29.3)	52 (38.2)	208 (28.0)	388
Treatment-emergent SAEs	125 (28.6)	51 (37.5)	205 (27.6)	381 (29.0)
Drug-related treatment-emergent SAEs	2 (0.5)	1 (0.7)	6 (0.8)	9 (0.7)
Discontinuation of study drug				
Any AEs	56 (12.8)	19 (14.0)	115 (15.5)	190
TEAEs	54 (12.4)	19 (14.0)	113 (15.2)	186
Drug-related TEAEs	5 (1.1)	5 (3.7)	9 (1.2)	19 (1.4)

Percentage was calculated using the number of patients in the column heading as the denominator.
1. TEAEs were defined as AEs that first occurred or worsened in severity on or after the first dose date of the double-blind study drug and up to and including 28 days post-last dose date of the double-blind treatment.

2. CTCAE severity: Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Life-threatening or disabling, Grade 5: Death related to the event.
3. Deaths due to adverse events were recorded starting on the date of the first dose of double-blind study drug and up to the end of the 28-day follow-up period. All deaths occurring after the 28-day follow-up period were captured in the survival follow-up period.
4. TEAEs of special interest were summarized based on pre-defined preferred terms of interest or pre-defined by Standardized MedDRA Queries.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Serious adverse event / deaths / other significant events

In set A in total, 264 (27.2%) patients had a treatment-emergent SAE: 178 (27.4%) patients in the anamorelin 100 mg group, and 86 (26.7%) patients in the placebo group. **Table 31** provides the details on SOCs/PTs for which the SAE was reported.

Table 31. Summary of Treatment-Emergent Serious Adverse Events by SOC/PT in Safety Set A

System Organ Class Preferred Term	**Placebo (N=213) n (%)**	**Anamorelin100mg (N=422) n (%)**	**Total (N=635) n (%)**
Patients with any treatment-emergent SAE	86 (26.7)	178 (27.4)	264 (27.2)
Blood and lymphatic system disorders	18 (5.6)	24 (3.7)	42 (4.3)
Anaemia	6 (1.9)	9 (1.4)	15 (1.5)
Febrile neutropenia	5 (1.6)	2 (0.3)	7 (0.7)
Leukopenia	0 (0.0)	1 (0.2)	1 (0.1)
Neutropenia	2 (0.6)	4 (0.6)	6 (0.6)
Pancytopenia	2 (0.6)	5 (0.8)	7 (0.7)
Thrombocytopenia	3 (0.9)	2 (0.3)	5 (0.5)
Cardiac disorders	8 (2.5)	10 (1.5)	18 (1.9)
Arrhythmia	1 (0.3)	0 (0.0)	1 (0.1)
Atrial fibrillation	2 (0.6)	2 (0.3)	4 (0.4)
Atial flutter	1 (0.3)	0 (0.0)	1 (0.1)
Atrial tachycardia	0 (0.0)	1 (0.2)	1 (0.1)
Cardiac arrest	2 (0.6)	0 (0.0)	2 (0.2)
Cardiac failure congestive	0 (0.0)	1 (0.2)	1 (0.1)
Cardiopulmonary failure	1 (0.3)	1 (0.2)	2 (0.2)
Ischaemic cardiomyopathy	0 (0.0)	1 (0.2)	1 (0.1)
Myocardial infarction	1 (0.3)	0 (0.0)	1 (0.1)
Pericardial effusion	1 (0.3)	2 (0.3)	3 (0.3)
Pericarditis constrictive	0 (0.0)	1 (0.2)	1 (0.1)
Tachycardia paroxysmal	0 (0.0)	1 (0.2)	1 (0.1)
Gastrointestinal disorders	6 (1.9)	13 (2.0)	19 (2.0)
General disorders and administrative site conditions	4 (1.2)	19 (2.9)	23 (2.4)
Asthenia	0 (0.0)	2 (0.3)	2 (0.2)
Death	1 (0.3)	8 (1.2)	9 (0.9)
Fatigue	0 (0.0)	1 (0.2)	1 (0.1)
General physical health deterioration	1 (0.3)	4 (0.6)	5 (0.5)
Pain	1 (0.3)	0 (0.0)	1 (0.1)
Pyrexia	1 (0.3)	4 (0.6)	5 (0.5)
Hepatobiliary disorders	2 (0.6)	0 (0.0)	2 (0.2)
Cholecystitis	1 (0.3)	0 (0.0)	1 (0.1)
Hepatic failure	1 (0.3)	0 (0.0)	1 (0.1)
Infections and infestations	14 (4.3)	27 (4.2)	41 (4.2)
Pneumonia	5 (1.6)	12 (1.8)	17 (1.7)
Metabolism and nutrition disorders	5 (1.6)	16 (2.5)	21 (2.2)

System Organ Class Preferred Term	Placebo (N=213) n (%)	Anamorelin100mg (N=422) n (%)	Total (N=635) n (%)
Decreased appetite	1 (0.3)	1 (0.2)	2 (0.2)
Dehydration	2 (0.6)	2 (0.3)	4 (0.4)
Diabetes mellitus	0 (0.0)	3 (0.5)	3 (0.3)
Diabetes mellitus inadequate control	0 (0.0)	1 (0.2)	1 (0.1)
Electrolyte imbalance	0 (0.0)	1 (0.2)	1 (0.1)
Failure to thrive	2 (0.6)	0 (0.0)	2 (0.2)
Hypercalcaemia	0 (0.0)	1 (0.2)	1 (0.1)
Hyperglycaemia	0 (0.0)	4 (0.6)	4 (0.4)
Hyperkalaemia	0 (0.0)	1 (0.2)	1 (0.1)
Hypertriglyceridaemia	0 (0.0)	1 (0.2)	1 (0.1)
Hypocalcaemia	0 (0.0)	1 (0.2)	1 (0.1)
HYypokalaemia	0 (0.0)	1 (0.2)	1 (0.1)
Musculoskeletal and connective tissue disorders	1 (0.3)	2 (0.3)	3 (0.3)
Back pain	1 (0.3)	1 (0.2)	2 (0.2)
Bone pain	0 (0.0)	1 (0.2)	1 (0.1)
Musculoskeletal chest pain	0 (0.0)	1 (0.2)	1 (0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	34 (10.6)	70 (10.8)	104 (10.7)
Epiglottic carcinoma	0 (0.0)	1 (0.2)	1 (0.1)
Gastric cancer	0 (0.0)	1 (0.2)	1 (0.1)
Neeoplasm progression	34 (10.6)	69 (10.6)	103 (10.6)
Nervous system disorders	1 (0.3)	6 (0.9)	7 (0.7)
Cerebrovascular accident	0 (0.0)	1 (0.2)	1 (0.1)
Cerebrovascular insufficinecy	0 (0.0)	1 (0.2)	1 (0.1)
Convulsion	1 (0.3)	1 (0.2)	2 (0.2)
Ischaemic stroke	0 (0.0)	1 (0.2)	1 (0.1)
Metabolic encephalpathy	0 (0.0)	1 (0.2)	1 (0.1)
Nervous system disorders presycnope	0 (0.0)	1 (0.2)	1 (0.1)
Psychiatric disorders	0 (0.0)	4 (0.6)	4 (0.4)
Agitation	0 (0.0)	1 (0.2)	1 (0.1)
Completed suicide	0 (0.0)	1 (0.2)	1 (0.1)
Cofusional state	0 (0.0)	1 (0.2)	1 (0.1)
Mental status changes	0 (0.0)	1 (0.2)	1 (0.1)
Renal and urinary disorders	3 (0.9)	0 (0.0)	3 (0.3)
Hamaturia	1 (0.3)	0 (0.0)	1 (0.1)
Renal failure	1 (0.3)	0 (0.0)	1 (0.1)
Urinary tract obstruction	1 (0.3)	0 (0.0)	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	12 (3.7)	27 (4.2)	39 (4.0)
Chronic obstructive pulmonary disease	3 (0.9)	4 (0.6)	7 (0.7)
Dyspnoea	3 (0.9)	1 (0.2)	4 (0.4)
Dyspnoea exterional	0 (0.0)	1 (0.2)	1 (0.1)
Epistaxis	0 (0.0)	2 (0.3)	2 (0.2)
Haemoptysis	2 (0.6)	1 (0.2)	3 (0.3)
Hypoxia	0 (0.0)	1 (0.2)	1 (0.1)

In set C, 381 (29.0%) patients had a treatment-emergent SAE**: 205 (27.6%)** patients in the **anamorelin 100 mg** group, and **125 (28.6%)** patients in the **placebo** group (**Table 32**).

Table 32. Summary of Treatment-Emergent Serious Adverse Events (≥ 3 Patients in Any Treatment Group) by SOC/PT in Safety Set C

System Organ Class Preferred	Placebo N = 437 n (%)	Anamorelin 50 mg N = 136 n (%)	Anamorelin 100 mg N = 743 n	Total N = 1316 n (%)
Patients with any treatment-emergent	125 (28.6)	51 (37.5)	205 (27.6)	381 (29.0)
Blood and lymphatic system	21 (4.8)	5 (3.7)	26 (3.5)	52 (4.0)
Anaemia	7 (1.6)	3 (2.2)	10 (1.3)	20 (1.5)
Febrile neutropenia	5 (1.1)	2 (1.5)	2 (0.3)	9 (0.7)
Neutropenia	3 (0.7)	0 (0.0)	5 (0.7)	8 (0.6)
Pancytopenia	2 (0.5)	0 (0.0)	5 (0.7)	7 (0.5)
Thrombocytopenia	3 (0.7)	0 (0.0)	2 (0.3)	5 (0.4)
Cardiac disorders	10 (2.3)	9 (6.6)	13 (1.7)	32 (2.4)
Atrial fibrillation	4 (0.9)	2 (1.5)	2 (0.3)	8 (0.6)
Cardio-respiratory arrest	0 (0.0)	4 (2.9)	1 (0.1)	5 (0.4)
Gastrointestinal disorders	10 (2.3)	5 (3.7)	18 (2.4)	33 (2.5)
Abdominal pain	1 (0.2)	0 (0.0)	3 (0.4)	4 (0.3)
Nausea	0 (0.0)	0 (0.0)	3 (0.4)	3 (0.2)
Vomiting	1 (0.2)	2 (1.5)	6 (0.8)	9 (0.7)
General disorders and administrative	15 (3.4)	16 (11.8)	27 (3.6)	58 (4.4)
Death	2 (0.5)	0 (0.0)	10 (1.3)	12 (0.9)
Disease progression	7 (1.6)	11 (8.1)	6 (0.8)	24 (1.8)
General physical health deterioration	1 (0.2)	0 (0.0)	4 (0.5)	5 (0.4)
Pyrexia	2 (0.5)	0 (0.0)	4 (0.5)	6 (0.5)
Infections and infestations	26 (5.9)	5 (3.7)	28 (3.8)	59 (4.5)
Pneumonia	12 (2.7)	3 (2.2)	13 (1.7)	28 (2.1)
Urinary tract infection	3 (0.7)	0 (0.0)	1 (0.1)	4 (0.3)
Metabolism and nutrition disorders	7 (1.6)	4 (2.9)	19 (2.6)	30 (2.3)
Dehydration	3 (0.7)	0 (0.0)	3 (0.4)	6 (0.5)
Diabetes mellitus	0 (0.0)	0 (0.0)	3 (0.4)	3 (0.2)
Hyperglycaemia	0 (0.0)	0 (0.0)	4 (0.5)	4 (0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	37 (8.5)	3 (2.2)	75 (10.1)	115 (8.7)
Neoplasm malignant	1 (0.2)	1 (0.7)	3 (0.4)	5 (0.4)
Neoplasm progression	34 (7.8)	0 (0.0)	69 (9.3)	103 (7.8)
Nervous system disorders	5 (1.1)	4 (2.9)	9 (1.2)	18 (1.4)
Convulsion	2 (0.5)	0 (0.0)	4 (0.5)	6 (0.5)
Respiratory, thoracic, and	21 (4.8)	10 (7.4)	32 (4.3)	63 (4.8)
Chronic obstructive pulmonary	3 (0.7)	1 (0.7)	5 (0.7)	9 (0.7)
Dyspnoea	5 (1.1)	2 (1.5)	3 (0.4)	10 (0.8)
Pleural effusion	3 (0.7)	2 (1.5)	2 (0.3)	7 (0.5)
Pulmonary embolism	2 (0.5)	1 (0.7)	8 (1.1)	11 (0.8)
Pulmonary haemorrhage	1 (0.2)	0 (0.0)	10 (1.3)	11 (0.8)
Respiratory failure	3 (0.7)	1 (0.7)	1 (0.1)	5 (0.4)

Nine (0.7%) patients in Set C had SAE which were classified as drug-related treatment-emergent SAE according the investigator's judgment: 6 (0.8%) patients in the anamorelin 100 mg group and 2 (0.5%) patients in the placebo group (**Table 33**).

Table 33. Study-Drug Related Treatment Emergent SAEs by System in Set C

Treatment	Preferred Term	Grade	Outcome
Placebo	Embolic Stroke	5	Fatal
Placebo	Anemia	3	Recovered
100 mg	Ischemic Cardiomyopathy	4	Recovered w Sequale
100 mg	Diabetes mellitus inadequate control	3	Recovered
100 mg	Blood Glucose Increased	3	Recovered
100 mg	Hypertriglyceridemia	4	Recovered
50	Anaemia	3	Recovered
100 mg	Death	5	Fatal
100 mg	Dyspnoea	5	Fatal

Events considered related to study drug treatment had relatedness categorized as possibly, probably or unknown.

Deaths

Studies 203/205(which investigated only the 50mg dose), 11.6% of subjects had an AE leading to death on active and 4.5% on placebo. For study 206 the rates were 6.3% on the 50mg dose, 10% on 100mg and 0 on placebo up to week 4, followed by 0, 2% and 0 for the stage between week 4 and week 12. In study 207 the proportion of patients with fatal SAEs was 22.4% on the 50mg dose, 17.8% on 100mg and 16.9% on placebo.

In study 301 the proportion of patients with any TEAE leading to death was 10.6% on anamorelin and 14.3% on placebo. Whilst in study 302 it was 12.1% and 8.1% and in 303 it was 7.3% and 7.8%.

Overall, 208 subjects (15.8%) died during the studies included in safety set C. The frequency of deaths in the anamorelin HCl 100 mg treatment group was 16.4% and 14.6% in the placebo group. Death was reported in 111 subjects (8.4%) in the SOC Neoplasm benign, malignant and unspecified, and in 38 (2.9%) subjects in the SOC General disorders and administration site conditions. Most of the subjects died due to disease progression in both treatment groups (10.1% and 9.2% of subjects in the anamorelin HCl 100mg group and placebo group, respectively). Twenty-eight deaths were also reported in the SOC Respiratory disorders and 14 deaths in the SOC Cardiac disorders.

Over the 12-month follow-up time in these studies, the percentage of subject deaths was 58.0% in the placebo group and 60.2% in the anamorelin group. Median survival time over 1 year was 9.17 months for the placebo group and 8.90 months for the anamorelin group. The hazard ratio (anamorelin vs. placebo) was 1.06 (p = 0.4691).

Adverse events of interest

Given the nature of ghrelin agonists and their expected pharmacodynamics and the findings from the trials conducted, the applicant identified the below adverse events of interest (AESI):

- Blood glucose increase
- Drug-Related Hepatic Disorders
- Cardiovascular events
- ECG abnormalities

• Oedema

• Phototoxicity

Table 36 summarizes AESI by SMQ category and preferred term that occurred in at least 2 subjects in the 100 mg anamorelin HCl group. Overall, there were 321 subjects (24.4%) that had an AE of special interest; 202 (27.2%) in the 100 mg anamorelin HCl group and 86 (19.7%) in the placebo group.

Table 34. Summary of Treatment-Emergent AESI in at least 2 patients treated with Anamorelin HCl 100 mg by Category and Preferred Term – Safety Population

Category Subcategory Preferred Term	Placebo N = 437 n (%)	Anamorelin HCl 50 mg N = 136 n (%)	Anamorelin HCl 100 mg N = 743 n (%)	Total N = 1316 n (%)
Patients with any TEAE of special interest	86 (19.7)	33 (24.3)	202 (27.2)	321 (24.4)
Blood glucose increased				
Hyperglycaemia/new onset diabetes mellitus SMQ	27 (6.2)	4 (2.9)	98 (13.2)	129 (9.8)
Blood glucose increased	1 (0.2)	0 (0.0)	9 (1.2)	10 (0.8)
Diabetes mellitus	6 (1.4)	1 (0.7)	22 (3.0)	29 (2.2)
Glycosuria	1 (0.2)	0 (0.0)	2 (0.3)	3 (0.2)
Glycosylated haemoglobin increased	1 (0.2)	0 (0.0)	5 (0.7)	6 (0.5)
Hyperglycaemia	20 (4.6)	3 (2.2)	69 (9.3)	92 (7.0)
Type 2 diabetes mellitus	0 (0.0)	0 (0.0)	4 (0.5)	4 (0.3)
Cardiovascular events				
Cardiac failure SMQ	3 (0.7)	4 (2.9)	6 (0.8)	13 (1.0)
Cardiac failure	2 (0.5)	1 (0.7)	3 (0.4)	6 (0.5)
Cardiopulmonary failure	1 (0.2)	0 (0.0)	2 (0.3)	3 (0.2)
Cerebrovascular disorders SMQ	2 (0.5)	0 (0.0)	5 (0.7)	7 (0.5)
Cerebrovascular accident	0 (0.0)	0 (0.0)	2 (0.3)	2 (0.2)
Ischemic heart disease SMQ	3 (0.7)	0 (0.0)	3 (0.4)	6 (0.5)
Coronary artery disease	1 (0.2)	0 (0.0)	2 (0.3)	3 (0.2)
Electrocardiogram				
Cardiac arrhythmias SMQ	13 (3.0)	5 (3.7)	17 (2.3)	35 (2.7)
Atrial fibrillation	8 (1.8)	3 (2.2)	11 (1.5)	22 (1.7)
Torsade de pointes/QT prolongation SMQ	0 (0.0)	1 (0.7)	2 (0.3)	3 (0.2)
Edema				
Haemodynamic oedema, effusions and fluid overload SMQ	28 (6.4)	25 (18.4)	45 (6.1)	98 (7.4)
Ascites	1 (0.2)	1 (0.7)	2 (0.3)	4 (0.3)
Oedema	1 (0.2)	0 (0.0)	2 (0.3)	3 (0.2)
Oedema peripheral	17 (3.9)	19 (14.0)	34 (4.6)	70 (5.3)
Pericardial effusion	2 (0.5)	0 (0.0)	2 (0.3)	4 (0.3)
Pleural effusion	8 (1.8)	4 (2.9)	9 (1.2)	21 (1.6)
Hepatic disorders				
Drug-related hepatic disorders SMQ – comprehensive search	32 (7.3)	7 (5.1)	79 (10.6)	118 (9.0)
Alanine aminotransferase increased	19 (4.3)	2 (1.5)	57 (7.7)	78 (5.9)
Ascites	1 (0.2)	1 (0.7)	2 (0.3)	4 (0.3)
Aspartate aminotransferase increased	20 (4.6)	3 (2.2)	41 (5.5)	64 (4.9)
Gamma-glutamyltransferase increased	2 (0.5)	0 (0.0)	9 (1.2)	11 (0.8)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	2 (0.3)	2 (0.2)
Hyperbilirubinaemia	0 (0.0)	1 (0.7)	6 (0.8)	7 (0.5)
International normalised ratio increased	2 (0.5)	0 (0.0)	2 (0.3)	4 (0.3)
Liver function test abnormal	0 (0.0)	2 (1.5)	3 (0.4)	5 (0.4)
Transaminases increased	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)

Table 35, summarizes the findings on AESI in the pivotal set A

Table 35. Overview on Treatment-Emergent Adverse Events Classified as Adverse Events of Special Interest by SOCs/PTs in Set A (Phase III trials)

Category Subcategory Preferred Term	Placebo (N=322) n (%)	Anamorelin 100mg (N=650) n (%)	Total (N=972) n (%)
Patients with TEAEs of Special Interest Any TEAEs	60 (18.6)	183 (28.2)	243 (25.0)
Drug-Related	15 (4.7)	59 (9.1)	74 (7.6)
Serious TEAEs	8 (2.5)	20 (3.1)	28 (2.9)
Drug-Related Serious TEAEs	0 (0.0)	3 (0.5)	3 (0.3)
Drug-Related NCI CTCAE Grade III/IV/V	2 (0.6)	9 (1.4)	11 (1.1)
Leading to Discontinuation	2 (0.6)	6 (0.9)	8 (0.8)
Blood glucose increased	20 (6.2)	92 (14.2)	112 (11.5)
Cardiovascular events	5 (1.6)	12 (1.8)	17 (1.7)
ECG	11 (3.4)	17 (2.6)	28 (2.9)
Oedema	12 (3.7)	35 (5.4)	47 (4.8)
Hepatic disorders	28 (8.7)	75 (11.5)	103 (10.6)
Phototoxicity	0 (0.0)	0 (0.0)	0 (0.0)

Laboratory findings

No clinically meaningful changes in haematology and biochemistry parameters were observed between treatment groups, except for increases in blood glucose, HbA1c, and ALT, which are presented in detail in this report.

Blood glucose, HbA1c

Data from baseline to worst post-baseline values for blood glucose in the integrated safety population showed that the majority patients with value ≤160 mg/dL at baseline (361 patients in the placebo group and 629 patients in the anamorelin HCl 100 mg group) had no postbaseline value above 160 mg/dL [328 (90.9%) of placebo, 467 (74.2%) of anamorelin HCl 100 mg patients]. Among the same group of patients with glucose levels ≤160 mg/dL at baseline, worst values of >160 – 250 mg/dL occurred in 30 (8.3%) patients in the placebo group and 128 (20.3%) patients in the anamorelin HCl 100 mg group.

A threshold of 250 mg/dL for blood glucose is considered clinically relevant, as this represents a definite pathological value, regardless of whether the patient was fasting or not. Considering this cut-off, 3 (0.8%) and 34 (5.4%) of patients with value below 160 mg/dL at baseline had a worst post-baseline value >250 in the placebo and the anamorelin HCl 100 mg groups, respectively. No patients in the placebo group and two patients in the anamorelin HCl group with value below 160 mg/dL at baseline had a worst baseline greater than 500 mg/dL.

Among the 30 patients in the placebo group with value >160 – 250 mg/dL at baseline, seven (23.3%) had at least one post-baseline greater than 250 mg/dl; no patient had postbaseline value worse than

500 mg/dL. Similarly, among 42 patients in the anamorelin HCl group with value >160 – 250 mg/dL at baseline, eleven (26.2%) patients had at least one post-baseline greater than 250 mg/dl, with one patient having a worst baseline greater than 500 mg/dL. One patient in the anamorelin HCl group with baseline value ranging from >250 to 500 mg/dL had a postbaseline value greater than 500 mg/dL.

To evaluate the potential role of anamorelin HCl in determining an increase of blood glucose levels, changes of circulating HbA1c levels were also analyzed. HbA1c is a reliable and reproducible indicator of blood glucose level over the two-three months prior to its assay and its levels are not influenced by fasting conditions, differently from measurements of glycemia.

Mean HbA1c values at baseline were similar in anamorelin HCl 100 mg and placebo groups and increased at Week 12 in the anamorelin HCl group, with a mean change from baseline of 0.480% whilst these levels were unchanged in the placebo group. Maximum increase from baseline was similar in either group (5.84% in anamorelin HCl vs. 5.30% in placebo).

Transaminases (ALT/AST) increase

The majority of patients in the placebo (71.4%) and in the anamorelin HCl group (63.0%) had a worst post baseline value lower than the upper limit of normal (ULN). A higher proportion of patients receiving anamorelin HCl 100 mg (25.2%) had a worst post baseline value ranging from >ULN to 3 times the ULN compared to placebo patients (18.1%). Likewise, a higher proportion of patients had worst post baseline values ranging from >3X to 5X ULN in the anamorelin HCl 100 mg group (3.6%) compared to placebo (1.4%). Similar frequencies of patients (0.7% and 0.5% patients, respectively) had elevations in the >5X to 20X ULN in anamorelin HCl and placebo groups while no patient had an elevation >20X ULN.

The trend was similar for AST. Most patients had a worst post-baseline value less than the ULN (65.7% and 62.3% for the placebo and anamorelin HCl 100 mg group). A total of 23.6% and 27.6% of patients in the placebo and 100 mg anamorelin HCl group, respectively, had worst post-baseline AST value from >ULN to 3X ULN. The frequency of patients with AST values 3 to 5X ULN worst values was 2.2% in the anamorelin HCl 100 mg group compared to 1.4% of patients treated with placebo. As with ALT, a similar proportion of patients had worst baseline values between 5 and 20X ULN in the anamorelin HCl 100 mg and placebo group and no patient in either group had a postbaseline value greater than 20X ULNSafety related to drug-drug interactions and other interactions

Discontinuation due to adverse events

TEAEs that led to discontinuation of study drug are reported overall in 186 (14.1%) patients: 113 (15.2%) patients in the anamorelin HCl 100 mg group, and 54 (12.4%) patients in the placebo group. Nineteen (1.4%) of these patients had a study drug-related TEAE that led to discontinuation of study drug: 9 (1.2%) patients in the anamorelin HCl 100 mg group, and 5 (1.1%) patients in the placebo group.

Discontinuation due to a TEAE occurred in 15.2% in the 100 mg anamorelin group and in 12.4% in the placebo group in safety set C.

The main reasons for discontinuation reported were progression of the disease (SOC: Neoplasms, benign, malignant and unspecified [6.2%]) followed by Gastrointestinal disorders (1.7%), and Respiratory, thoracic and mediastinal disorders (1.7%). At PT level the only event leading to discontinuation in more than 1% of patients was neoplasm progression (5.3%).

In the pivotal safety set A the frequency of TEAEs that led to treatment discontinuation was also higher in the anamorelin arm: 100 (15.4%) patients in the anamorelin 100 mg group and 42 (13.0%) patients in the placebo group. Five (0.8%) patients in the anamorelin HCl 100 mg group and 2 (0.6%) patients in the placebo group had a drug-related TEAE that led to discontinuation of study drug.

Extension Study HT-ANAM-303

An additional safety set (SET B) was defined to characterise the long term safety of anamorelin. This included 343 patients who received anamorelin HCl 100 mg during the initial both pivotal trial (included in Set A) and participated in the additional 12 week extension study HT-NAM-303. (Extended Exposure for 24 weeks, not integrated in general analyses). Exposure in this safety set is summarised in **Table 36.**

Table 36. Summary of exposure to study drug in Safety Population – Set B

Exposure Statistic/category	Placebo N = 167 n (%)	Anamorelin N = 343 n (%)	Total N = 510 n (%)
Extent of exposure (days) in HT-ANAM-303			
N	167	343	510
Mean (SD)	77.2 (21.28)	76.1 (23.42)	76.5 (22.73)
Exposure category n (%) in HT-ANAM-303			
≥ 4 weeks	161 (96.4)	318 (92.7)	479 (93.9)
≥ 8 weeks	144 (86.2)	293 (85.4)	437 (85.7)
≥ 12 weeks	109 (65.3)	221 (64.4)	330 (64.7)

Percentage was calculated using the number of patients in the column heading as the denominator.
Extent of exposure (days) = date of last dose – date of first dose + 1.
SD = standard deviation.

In total, 272 (53.3%) patients had at least 1 TEAE: 179 (52.2%) patients in the anamorelin HCl group and 93 (55.7%) patients in the placebo group. The results suggest that with an additional 12 weeks of exposure, the overall frequency of TEAEs was lower compared to the original studies.

Fourteen (2.7%) patients had at least 1 study drug-related TEAE: 12 (3.5%) patients in the anamorelin HCl group and 2 (1.2%) patients in the placebo group. TEAEs with a CTCAE grade of 3 or higher were well balanced between placebo and anamorelin HCl patients, and none of these were considered drug-related. Overall, there was a higher frequency of deaths in the placebo (13.2%) compared to anamorelin HCl group (10.2%); with a similar frequency considered TEAEs leading to death (7.8% and 7.3% in the placebo and anamorelin HCl groups). The frequency of treatment emergent SAEs was similar between treatment groups (12.6% and 12.8% in the placebo and anamorelin HCl groups, respectively) and none were considered related to the drug. Discontinuations due to TEAEs were also similar in frequency between the two study groups (6.6% and 6.4% in the placebo and anamorelin HCl groups, respectively).

The most commonly reported TEAEs in the anamorelin HCl group were anemia (48 [14.0%] patients), asthenia (20 [5.8%] patients), neutropenia (18 [5.2%] patients). The most commonly reported TEAEs in the placebo group were anemia (26 [15.6%] patients), and asthenia (14 [8.4%] patients. In addition, decreased appetite was reported as a TEAE by patients in both treatment groups (12 [3.5%] and 10 [6.0%]) of patients in the anamorelin HCl and placebo groups, respectively.

In total, 65 (12.7%) subjects had a treatment-emergent SAE: 44 (12.8%) subjects in the anamorelin HCl group and 21 (12.6 %) subjects in the placebo group. Compared to the two original studies, the frequency of treatment-emergent SAEs from both treatment groups were lower. No subjects had any study drug-related treatment-emergent SAE.

Overall, 38 subjects (7.5%) died during the long term extension study 303. The most commonly reported TEAE leading to death was neoplasm progression: 7 (4.2%) subjects in the placebo group and 16 (4.7%) subjects in the anamorelin group. Of note, none of the TEAEs leading to death were considered to be study drug-related.

The frequency of TEAEs of special interest was comparable between anamorelin HCl 100 mg and placebo groups, with 14.6% vs. 12.6% respectively. Higher frequencies of TEAEs were seen for the event category of Hepatic Disorders (6.4 % vs. 3.6%) and Blood Glucose Increase (5.5% vs. 3.6%).

The frequency of TEAEs in the categories of Cardiovascular events was 3.8% vs. 2.4% whereas for ECG events a higher proportion of patients in the placebo reported abnormalities compared to anamorelin HCl amorelin HCl group (4.2% vs. 1.2%). In general, no differences were observed for the events in the category Edema, with an overall frequency of 2.6% and 3.0% in the anamorelin HCl and placebo arms. As for the related TEAEs, hyperglycemia was reported for 1.2% and 0.0% of patients in the anamorelin HCl and placebo groups, while diabetes mellitus was experienced by one anamorelin HCl treated patient (0.2%).

Table 37. Summary of CTCAE Grade 3/4/5 (Experienced by ≥ 2% Patients in Either Treatment Group) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Population Set B

System Organ Class Preferred Term	Placebo N = 167 n (%)	Anamorelin N = 343 n (%)	Total N = 510 n (%)
Patients with any CTCAE Grade 3/4/5 TEAE	36 (21.6)	77 (22.4)	113 (22.2)
Blood and lymphatic system disorders	8 (4.8)	15 (4.4)	23 (4.5)
Anaemia	1 (0.6)	9 (2.6)	10 (2.0)
Neutropenia	4 (2.4)	4 (1.2)	8 (1.6)
General disorders and administration site conditions	11 (6.6)	22 (6.4)	33 (6.5)
Asthenia	5 (3.0)	12 (3.5)	17 (3.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7 (4.2)	19 (5.5)	26 (5.1)
Neoplasm progression	7 (4.2)	16 (4.7)	23 (4.5)
Respiratory, thoracic and mediastinal disorders	4 (2.4)	9 (2.6)	13 (2.5)
Dyspnoea	4 (2.4)	5 (1.5)	9 (1.8)

Blood Glucose increase at baseline of this extension study, 306 (89.2%) patients in the anamorelin HCl group and 164 (98.2%) patients in the placebo group had blood glucose levels ≤ 160 mg/dL. As presented in in Study HT-ANAM-303 Table 34, among patients with baseline levels ≤ 160 mg/dL, 21 patients (6.1%) and five patients (3.0%) shifted to >160-250 mg/dL in the anamorelin HCl 100 mg and placebo groups, respectively; in the same group of patients with baseline levels ≤ 160 mg/dL three patients (0.9%) and one patient (0.6%) shifted to >250-500 mg/dL. No patient shifted to >500 mg/dL in either arm.

In the anamorelin HCl 100 mg group, two (0.6%) patients with baseline levels >160-250 mg/dL, shifted to >250-500 mg/dL and no patient shifted to>500 mg/dL. In the placebo group, no patient with baseline levels >160-250 mg/dL shifted to a worse level.

Transaminases (ALT/AST) Increase. Examination of laboratory data over the course of the 12-week extension study indicated that ALT increases > 3 × ULN on at least one occasion occurred in eight (2.5%) patients in the anamorelin HCl group and one (0.6%) patient in the placebo group post-baseline. Four (1.3%) patients in the anamorelin HCl group and three (1.9%) patients in the placebo group had a post-baseline elevation in AST > 3 × ULN on at least one occasion.

2.6.1. Discussion on clinical safety

The applicant focussed its analysis on safety of anamorelin on data from the 100 mg dose for phase 2 and phase 3 studies, which were also presented separately.

The twelve Phase 1 studies and the additional 12-week safety extension study (HT-ANAM-303) were not integrated into the database. The latter was however presented in order to provide long term safety results for anamorelin (Set B).

However given that a substantial proportion of patients survived beyond 6 months (the end of the extension phases of the two phase III trials), the information provided by Set B, to assess long term safety is considered inadequate.

Assessment of safety in an advanced cancer population setting, as the intended target population for Adlumiz, is especially challenging due to the potential occurrence of many adverse events which may occur due to the background disease or concomitant treatment. In such cases of particular importance in the characterization of the safety of a product are concerns which have been identified in non-clinical models and during the early clinical development.

From the non-clinical data, blood glucose increase in terms of manifestation or worsening of diabetes mellitus, and in particular cardiovascular events and arrhythmias due to Na+ channel inhibition as well as hepatotoxicity were identified to represent the main toxicities. Furthermore, increase in peripheral oedema due to unknown reasons was identified in phase II as a safety concern. Therefore, differences observed for the risk in these AESI are very important, while detection of other safety signals in a relative small population of advanced cancer patients concomitantly treated for their background disease presents with many difficulties.

Analyses of TEAEs of special interest (AESIs) show relatively large differences between both arms, not in favour for anamorelin: Blood Glucose Increase (14.2% vs. 6.2%) and Drug-Related Hepatic Disorders (11.5% vs. 8.7%) seemed to be the most frequent important events, lower frequencies and differences between the groups were also seen for edema. The increases in ALT which were observed are of particular concern. This is emphasised in the data from study 303, in which higher rates of ALT, AST, alkaline phosphatase and GGT increases were seen which are indicative of hepatic damage on active.

Blood glucose levels increased and increase in liver transaminases were included in the proposed Risk Management Plan as important identified risks. Overall, hyperglycemia and oedema events seemed to be manageable toxicities. The same may be presumed with respect to hepatotoxicity, as no case fulfilling Hy's law have been reported so far.

Comparing the cumulative drug dose it seems that exposure in both analysed safety sets [pivotal set A) supportive Set C= all cancer patients in phase II and III)] was slightly lower in the 100 mg patients compared with placebo patients. Although the difference was small, the lower exposure could be suggestive of a lower tolerability and clinically relevant toxicity. This is further supported by a higher discontinuation rate due to TEAEs in the anamorelin treated patients [Set A:100(15.4%) vs. P:42

(13.0%)]. With respect to the SAEs observed, there was also a higher rate of pulmonary emboli and haemorrhage.

The CHMP also noted that in the phase 3 studies the rates of any TEAEs (A: 78% vs. P:73,6%), SAEs (A:27.4% vs. P:26.7%) and also TEAEs leading to death (A:16.2% vs. P:15.5%) were consistently higher in anamorelin treated patients compared with placebo. An increase in AEs leading to death was also seen in all the phase 2 studies.

The pattern of higher AE rates is also reflected in those with grade 3 or higher. The 50mg dose also shows a substantially higher AE rate than placebo and the 100mg dose. The 100mg dose has rates similar to that of placebo.

Cardiotoxicity, the most important toxicity in animals, is the only AESI for which an impact on mortality can be clearly hypothesized. Raw frequency of TEAEs in the categories of Cardiovascular and ECG Events abnormalities in general were assessed to be similar or even somewhat lower in the 100 mg anamorelin group compared to placebo, though concerns have been raised on the reliability of the safety data collected in the phase III trial. Focusing on the details, it is concerning that the most dangerous arrhythmic events are reported exclusively in the anamorelin groups. The observation of 3 events in the SMQ “Torsade de point” / ventricular tachycardia in a small population of about 900 patients is a cause for concern.

The thorough QT study confirmed anamorelin’s cardiac sodium and hERG channel blocking characteristics. Results shown that with 400mg an unexpected high QRS interval widening in one subject occurred, with maximum mean QRS change from baseline of 87ms (~90% increase from baseline). While QTcF was only slightly affected, PR and QRS intervals were significantly prolonged, at least at doses >100mg. Cardiac effects seem independent from maximal plasma concentrations but occur about 4 hours delayed, which makes their timely clinical assessment in real life difficult. As arrhythmias were also the predominant toxicity in animals and increase mortality in dogs, it cannot be excluded that underreporting occurred in the study and significant events were not detected. Moreover, inhibition of CYP3A4 leads also to a significant increase in plasma concentration and thus also may have increased the risk during the studies due to concomitant medication.

Furthermore, sudden deaths events often associated with cardiac arrhythmias/QT prolongation are observed. It is acknowledged that identification of these cases in a NSCLC population may be difficult as death is an expected event in nearly all of these advanced cancer patients.

Overall, 208 subjects (15.8%) died during the studies included in safety set C. Over the 12-month follow-up time in these studies, the percentage of subjects who died was 58.0% in the placebo group and 60.2% in the anamorelin group. Median survival time over 1 year was 9.17 months for the placebo group and 8.90 months for the anamorelin group. The CHMP noted that with the exception of study 301 and its extension 303, all of the other phase 2 and 3 studies reported more AEs leading to death on treatment than on placebo which is of particular concern.

With respect to the arrhythmia risk, which had been identified early in the clinical development programme it was surprising that ECG monitoring was only performed twice post baseline during the 12 weeks and whether this was adequate.

The CHMP also expressed its concerns, that despite the fact that in the pivotal study population >75 % received concomitant disease modifying chemotherapy/immunotherapy and approx. 10% received concomitant radiotherapy a relatively low number of total adverse events and chemotherapy-related AEs (e.g. haematotoxicity) was reported compared to what can typically be expected in chemotherapy studies.

These concerns were further compounded by the GCP inspection reports which could not confirm GCP compliance in relation to the collection and reporting of SAEs in several investigator sites from the two pivotal phase III studies. Consequently, the inspection report concluded that safety data reported in the clinical study reports cannot be recommended for assessment.

Additional expert consultation

Two patients with lung cancer, one of which had experienced cachexia during the course of his disease, participated in an oral explanation at CHMP where the applicant addressed the outsanding issues. The patient representatives expressed their concerns over the important reported risks in association with anamorelin use, especially in view of the frailty of the patients for which anamorelin is intended to be used in.

2.6.2. Conclusions on the clinical safety

The CHMP noted that significant toxicity was consistently observed as illustrated by the higher number of TEAEs, SAEs, patients discontinued and especially by the higher number of deaths in patients treated with anamorelin compared to those on placebo. The areas of concern which were identified were hyperglycaemia and diabetes, hepatic events and especially cardiotoxicity which could provide an explanation for the imbalance of fatal events observed in the clinical development programme for anamorelincompared to placebo.

The CHMP however noted that a comprehensive assessment of safety at this stage was not possible. This is due to the limited size of the safety database and in particular the dataset provided to characterise the long term safety of anamorelin and especially the concerns raised by the GCP inspection which does not allow to fully characterise the risks associated with the use of anamorelin in patients with NSCLC.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan version:

The PRAC considered that the risk management plan version 1.3 could be acceptable if the applicant implements the changes to the RMP as specified in the 2nd Day 180 overview updated joint CHMP/PRAC assessment report, RMP section.

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan for Adlumiz cannot be agreed at this stage.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The applicant compared the structure of anamorelin with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers anamorelin to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union. However, in light of the negative opinion, new active substance status is not applicable at this stage.

2.10. Product information

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use. Howvere, Due to the aforementioned concerns a satisfactory package leaflet cannot be agreed at this stage.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Cancer cachexia occurs commonly in patients with cancer before death and is characterized by loss of appetite and/or an aversion to food (anorexia), loss of weight, asthenia, and a poor prognosis. Weight loss in particular is a significant predictor of chemotherapy-related toxic effects. Cachexia can also have detrimental effects on the patient's quality of life, affecting all members of the surrounding support network.

3.1.2. Available therapies and unmet medical need

Unmet medical need in this condition is recognised as there are no widely approved drugs for the treatment of cancer cachexia. Steroid hormones, and in particular corticosteroids have been shown to be effective in stimulating appetite. These however are also associated with significant safety concerns which are especially important given the frail population of this condition.

3.1.3. Main clinical studies

Two phase III pivotal studies (301 and 302) and their corresponding extensions were submitted to support the use of anamorelin in cachexia in NSCLC. The dose used in those trials was 100mg once daily.

3.2. Favourable effects

Changes in lean body mass have been shown across the presented studies to be statistically superior to placebo with anamorelin. The difference from placebo across the studies was around 1.5 kg of LBM (being 3-4% of median baseline LBM in the pivotal trials).

The secondary QoL endpoint A/CS, the Anorexia/Cachexia subscale of the FAACT, showed superiority for anamorelin over placebo in the pivotal studies (LS mean [95% CI] 2.21 [0.99, 3.42] and 2.14 [0.81, 3.47] respectively).

In the subgroup of patients with BMI < 20 kg/m2 the difference from placebo pooling both studies was 1.71 kg of LBM. A treatment effect was also seen on the changes from baseline in FAACT A/CS and FACIT-F Fatigue domain scores (mean difference from placebo [95% CI] 5.27 [2.11, 8.43] and 3.94 [0.56, 7.32] respectively).

3.3. Uncertainties and limitations about favourable effects

The co-primary endpoint change in handgrip strength (HGS) failed to show statistical significance or any benefit over placebo in both pivotal trials (301 and 302). This endpoint had also failed in two phase II studies (206 and 207). It is therefore plausible that anamorelin does not exhibit the efficacy required to change handgrip strength in these subjects. The failure of the co-primary strictly renders the studies failed and means that the data from the endpoints after those should not be considered.

In Scientific Advice sought by the company prior to submission of this application, CHMP had recommended “demonstration of a clear effect on one objective variable reliably measuring anabolic drug activity combined with one adequately validated subjective variable ensuring patient relevance”, which is e.g. ‘change in LBM’ in combination with a well-established and validated QoL endpoint. As the applicant did not adapt study design accordingly, due to the already ongoing pivotal studies while seeking advice, significant evidence of benefit from the QoL endpoints would be required to overcome the failed co-primary endpoint.

Only in the SAP for the pivotal trials the applicant split the 2 secondary endpoints measuring QoL the well-known instruments FAACT and FACIT-F - into 8 secondary QoL endpoints (FAACT: FAACT total score, FAACT TOI, A/CS, SEA and FACIT-F: FACIT-F total score, FACIT-F TOI, fatigue domain, SEF). For further interpretation it is important to know, that SEA is a sub-score of A/CS, which is a sub-score of FAACT TOI, which is a sub-score of FAACT total score. The same applies to the FACIT-F related endpoints.

No strategy to control for multiple testing was applied, although 8 QoL instruments were tested as secondary endpoints. Furthermore, QoL analyses were only based on the MITT and PP population instead of inclusion of all randomized patients in the analysis which would have guaranteed that the randomization was maintained. A selection leading to biased estimates cannot be excluded for analyses based on MITT and PP population. In addition, no minimally important difference (MID) was defined prospectively for the particular QoL endpoints, the MIDs were only discussed retrospectively with literature.

For the interpretation of QoL results, the method applied for analysis aims at estimation of the treatment effect that would have been observed if all patients had survived until week 12 and all patients had been fully adherent to treatment, which is likely to have overestimated the benefit.

Six out of the eight secondary endpoints regarding QoL described above failed statistically, including all QoL endpoints measuring fatigue, which is an important symptom affecting QoL of cachectic tumour patients. Also FAACT total score did not reach statistical significance in both pivotal trials.

The only QoL endpoints reaching statistical significance in both pivotal trials were the FAACT sub-scores A/CS and its newly developed sub-score SEA. Notably both did not reach the MID known from literature. Furthermore the SEA (simplified evaluation of appetite) QoL instrument – consisting of the 4 most responsive items of A/CS – was developed and validated within one of the pivotal trials (302) and published only after unblinding of the data of the pivotal trials. As a consequence SEA score has to be seen as very questionable for interpretation of the pivotal trial results.

Overall, the QoL measures used across the development programme have consistently failed to show statistical significance (apart from the one described above) and none have managed to demonstrate a clinically meaningful change in favour of anamorelin, also considering the post hoc prioritisation of sub-scales which can lead to bias in estimation. Given this, it is difficult to see what benefits the subjects in the studies on active gained, even despite the changes in lean body mass.

The dose selection is called into question. Study 207 shows no compelling evidence that 100mg was any better than 50mg, especially taking into account the failure of the co-primary in the study. Looking at the mean change from baseline for bodyweight with the 100mg dose, it can be seen that bodyweight was maintained, with no significant increase. This is reflected in the 50mg dose as well. Therefore no clear meaningful difference between the doses has been discerned.

The larger treatment effects seen in the subgroup of patients with BMI < 20kg/m2 come from a post-hoc analysis and since the randomisation was not stratified by this factor, it is possible that differences in baseline characteristics could have contributed to the differences seen between treatments. Therefore it is not clear how much of the effect can be attributed to the treatment. Furthermore it is not clear how many subgroups the applicant investigated before settling on this one as the most promising. It is well know that some differences between treatments will occur due to chance and therefore in some subgroups the effect may appear more pronounced. Without replication in a separate study it is not possible to establish whether this is just a chance finding.

3.4. Unfavourable effects

The safety profile identified in non-clinical models is aligned with the observed safety profile in the clinical studies. A significant safety risk of anamorelin in the human target population seems plausible but the safety data currently available are not sufficient due to the overall size of the database and issues over GCP compliance to allow valid assessing of the risk in the target population.

Rates of TEAEs, AESI and SAEs and deaths are consistently higher in anamorelin treated patients in comparison with placebo in the pivotal safety population. This characterises an increase of toxicity and a clinical relevant safety risks during treatment with anamorelin. Differences were observed comparing the phase 3 rates of any TEAEs (A: 78% vs. P:73,6%), SAEs (A:27.4% vs. P:26.7%) and also TEAEs leading to death in all clinical studies (A: 16.4% P: 14.6%).

There is a signal that anamorelin could increase the risk for life-threatening cardiac arrhythmias. The reporting of 3 events in the SMQ “Torsade de point”/ventricular tachycardia exclusively in anamorelin treated patients is highly concerning and it cannot be excluded that the trends for increased rate of on-treatment mortality observed is due the drug’s intrinsic pharmacodynamic properties (Na-channel interaction leading to a significant QRS widening).

Also from the pharmacodynamics an increased tumour progression could be supposed. Unfortunately this issue cannot be further assessed, since the applicant did not define this event as an adverse event of special interest to adequately investigate it.

The adverse event data also showed a potential association between anamorelin and hepatic disorders, as illustrated by changes in ALT. These changes whilst not usually extreme, were accompanied with increases in other liver function tests including AST, alkaline phosphatase and GGT. These changes are concerning given that they are occurring in a group of subjects who may already have hepatic impairment due to treatment or hepatic metastases.

A disparity in the rates of pulmonary embolus and pulmonary haemorrhage is also seen, with higher rates with anamorelin.

3.5. Uncertainties and limitations about unfavourable effects

Following the conclusion of the GCP inspection report which was requested by the CHMP, there are significant concerns regarding the under-reporting and reliability of the submitted safety data.

Further concerns are raised from the total number of adverse events reported which in view of the pivotal study population in which >75 % received concomitant disease modifying chemotherapy/immunotherapy and approx. 10% received concomitant radiotherapy a higher rate of total adverse events and chemotherapy-related AEs (e.g. haematotoxicity) would have been expected.

The assessment of ECG related TEAEs is not fully conclusive because the applicant did not implement sufficient methods to assess the increased arrhythmia risk in the safety investigation schedules. Although arrhythmias are related to anamorelin's pharmacodynamics, ECGs were only performed twice after screening during the 12 weeks of study duration and more sensitive methods were not included.

Anamorelin may lead to an increased tumour progression in the target population, but the risk is not clearly assessable, as no long-term data are available and therefore no definitive conclusion on the influence of anamorelin on tumour growth can be drawn.

Due to the dose used in all non-clinical studies there is a lack of the appropriate safety margins which could possibly allow exclusion of the findings from non-clinical data to humans.

Drug–drug interactions in the applied target population are insufficiently clinically characterized, but important due to the high need for concomitant medication in advanced cancer patients.

There are also concerns that anamorelin is hepatically metabolised and little information has been generated by the applicant of the pharmacokinetics or safety in those with hepatic impairment of any grade. There are therefore significant safety concerns that anamorelin causes hepatic damage and in hepatic impairment may cause higher overall exposure.

No other discussions of special populations beyond the elderly are made, including renal and hepatic impairment.

As a result of nonclinical pharmacology studies it has to be concluded that anamorelin is known to act like a class 1 antiarrhythmic agent on the sodium-channel and has the potential to increase a cardiovascular risk in humans. The thorough QT study revealed an effect of anamorelin on QT at doses of around 300mg effects. This is of concern given the lack of study of the PK in hepatic impairment and the lack of study of potential for inhibited metabolism with drug interaction, it is possible that plasma concentrations could reach levels similar to the 400mg dose and therefore QRS or QT prolongation effects may be seen.

3.6. Effects Table

Table 38. Effects Table for Adlumiz in the treatment of anorexia, cachexia or unintended weight loss in adult patients with non-small cell lung cancer (data cut-off: 28 January 2014).

Effect	Short description	Unit	Anamorelin	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Lean Body Mass	Change from baseline measured by Dual Energy X-Ray Absorptiometry Scans	kg	1.16 1.25	-0.37 -0.46	Small effect size of uncertain clinical relevance, no correlation with other endpoints Larger effect size in sub-population but sub-group prioritised only post-hoc	Pooled analysis of studies 301/302 Pooled analysis for of studies 301/302 in patients with a BMI <20 kg/m^2
Handgrip strength	Change of the Non-Dominant Hand from Baseline Over 12 Weeks	Kg	1.46 -1.49	0.48 -0.95	No statistical difference between placebo and anamorelin	Study 301 Study 302
Quality of Life Measures	FAACT-total score FACIT-F	N/A	6.46 2.02	3.78 -0.05	The validated QoL measures including FACIT-F and FAACT failed to show statistical significant difference from placebo. No perceived QoL benefit can be related to the LBM results.	Study 301
Unfavourable Effects						
Death		%	16.4	14.6	Small differences, difficult to interpret due to confounding by underlying cancer. Consistent effect across individual studies	Integrated safety set C
Cardiac toxicity and arrhythmia	Torsade de pointes/ QT prolongation SMQ	N	2	0	QTc changes were seen at doses of 300mg and above in the thorough QT	

Effect	Short description	Unit	Anamorelin	Control	Uncertainties / Strength of evidence	References
					study and further supported by non-clinical data.	
Hepatic damage	Drug-related hepatic disorders SMQ	%	10.6	7.3	ALT rises seen across the studies are of concern and indicate hepatic damage.	

Abbreviations: ALT= Alanine transaminase, BMI= Body mass index, FAACT=functional assessment of anorexia/cachexia therapy (FACT-G + A/CS), FACIT-F=functional assessment of chronic illness therapy - fatigue (FACT-G + fatigue subscale), SMQ= Standardised MedDRA Query

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In this palliative setting, whilst the moderate changes in comparison to placebo in body mass can be recognised, correlation to meaningful changes in QoLwould be important and have not been demonstrated.

An increased toxicity was consistently observed as illustrated by the higher incidence of TEAEs, SAEs, patients who discontinued due to TEAEs and in particular by more on-treatment deaths in the anamorelin patients compared to placebo. There are signals for clinically relevant toxicity which for a medicine intended for palliation in terminally ill cancer patients is of concern.

3.7.2. Balance of benefits and risks

The failure of the co-primary endpoints in both pivotal studies and the modest changes in body mass make it difficult to perceive clinically relevant efficacy benefit from treatment with anamorelin. Two accepted QoL questionnaires (FAACT and FACIT-F) were used as secondary endpoints, but were not able to clinically nor statistically demonstrate benefit on treatment when compared to placebo. The lack of correlation of the modest benefits on body mass with the many QoL measures used makes it difficult to see what treatment does to improve quality of life over placebo.

The lack of significant efficacy, paired with concerns about toxicity, from a safety database that is not adequate for assessment means that there is a negative balance in the benefit-risk assessment.

During the procedure the applicant introduced a post-hoc approach to focus on a subpopulation of the pivotal 301 + 302 trials, namely patients with BMI <20 kg/m2. This subgroup is exploratory and not acceptable to draw confirmatory conclusions. It is well known that drawing formal conclusions on efficacy in a subgroup are likely to be unreliable, in particular for a failed trial. Furthermore, it needs to be taken into consideration that the subgroup is small, implying that meaningful assessment of B/R based on this subgroup is uncertain. Reliable replication of evidence for this subgroup from independent trials is not available.

Only in secondary QoL endpoints, a more pronounced difference was observed. However, the post-hoc selection of a subgroup with a more pronounced effect than overall is associated with a high risk of selection bias. It should also be noted that the subgroup of patients with BMI < 20 kg/m² was even not a pre-specified subgroup but defined post-hoc, which means that concerns on a data-driven selection are even higher than usual. As the randomization was not stratified by BMI, there is also a risk of imbalances for baseline risk factors between treatment groups in this subgroup. Imbalances in the baseline score for the PRO instruments were already observed in the analyses presented, indicating that the patient populations were not consistent across treatment arms.

3.8. Conclusions

The overall B/R of Adlumiz (anamorelin) is considered negative by CHMP.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Adlumiz) in the treatment of of anorexia, cachexia or unintended weight loss in adult patients with non-small cell lung cancer (NSCLC) and Body Mass Index (BMI) < 20 kg/m^2, the CHMP considers by consensus that the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product. The CHMP considers that:

- Given the marginal effect on LBM without showing a reliable and clinically relevant effect on patient functioning or QoL, the therapeutic efficacy of anamorelin is not established.
- Restricting the indication to the subgroup with Body Mass Index < 20 kg/m^2 is not considered acceptable given that this subgroup was prioritised post-hoc and confirmatory conclusions of the benefit -risk based on this subgroup analyses cannot be made.
- There are significant concerns regarding evaluation of the safety profile of Adlumiz based on the overall small size of the clinical safety database, and in particular in light of the conclusion from the GCP inspection that the integrity of the safety database is compromised. The trends of higher morbidity and on treatment mortality rates across the clinical studies and the signals for cardiovascular events and hepatoxicity observed in pre-clinical studies with limited safety margins in relation to the doses used in human studies cannot be comprehensively evaluated.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, and risk management plan cannot be agreed at this stage.

5. Re-examination of the CHMP opinion of 15 May 2017

Following the CHMP conclusion that Adlumiz was not approvable as its efficacy had not been established and due to the uncertainities that did not allow to draw definitive conclusions about its safety profile , the applicant submitted detailed grounds for the reexamination of the grounds for refusal.

Following a request from the applicant at the time of the re-examination, the CHMP convened a

Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response.

Detailed grounds for re-examination submitted by the applicant

The applicant presented in their submission the following grounds for re-examination:

CHMP Ground #1

- Given the marginal effect on LBM without showing a reliable and clinically relevant effect on patient functioning or QoL, the therapeutic efficacy of anamorelin is not established.

Summary of the Applicant`s position:

The anamorelin pivotal clinical program (named ROMANA) is the largest of its kind, enrolling 979 patients, with treatment totalling up to 24 weeks and including two double-blind, placebo-controlled, Phase 3 pivotal studies (Studies HT-ANAM-301 and HT-ANAM-302) of 12-weeks duration with a 12-week optional safety extension study (Study HT-ANAM-303) in advanced NSCLC patients with cachexia. The efficacy and safety of anamorelin in Phase 3 studies are also supported by data from four Phase 2 studies in 361 patients, 226 of whom had NSCLC.

The clinical benefit of anamorelin was consistent in both pivotal studies as shown by a rapid and sustained increase of lean and fat mass (and, consequently, body weight) and a substantial improvement in cancer anorexia symptoms/concerns as measured by the Functional Assessment of Anorexia/Cachexia Therapy additional concern domain (FAACT A/CS), addressing anorexia/cachexia-specific items.

LBM

The LBM endpoint was consistently and significantly improved across all body compartments in both Phase 3 studies, both in the overall population and even more so in patients with BMI < 20 kg/m^2, underscoring the anabolic activity of anamorelin.

The increase in fat mass along with increase in LBM indicates restoration of the metabolic abnormalities of cachexia by positively shifting from a catabolic energy wasting to energy balance. Additionally, clinically meaningful improvements in the anorexia-cachexia patient-reported questionnaires from the FAACT A/CS domain score were observed (including symptoms related to loss of appetite and early satiety, and patient's and family caregivers' concerns related to weight loss, body image and general health).

DXA measurement of lean and fat mass body composition assessment was conducted in the two pivotal Phase 3 studies HT-ANAM-301 and HT-ANAM-302. In both studies LBM increased from baseline over 12 weeks in the anamorelin group compared to a decrease in the placebo group; the difference of median changes between placebo and anamorelin was 1.46 kg in Study HT-ANAM-301 and 1.63 kg in Study HT-ANAM-302 and was highly statistically significant ($p < 0.0001$) in both studies.

In patients with advanced cancer, decline rate is accelerated with LBM loss ranging 0.14-0.20 kg per month (Wallengren et al. 2015), and is more evident in patients with progressive compared with stable disease. In this frame, the observed treatment effect with anamorelin of 1.46-1.63 kg over 12 weeks of treatment should be considered outstandingly large as it reverses on average the effect of 7-10 months of disease-related loss of lean mass. Therefore, the reiterated statement from the CHMP that the effect on LBM is marginal is not founded on available science. While the CHMP previously commented on the fact that a different assumption for a treatment effect of 2.0 kg was made in the

original protocol and Statistical Analysis Plans for ROMANA studies, it should be noted that this assumption was actually made for the HGS endpoint, not LBM.

Furthermore, recent interventional studies in NSCLC patients have also provided evidence that LBM increases of ≥ 1 kg are clinically meaningful based on longer survival compared to patients who do not gain at least 1 kg of LBM (Crawford et al. 2014). Pooled data from the two Phase 3 pivotal studies show that more than 50% of patients receiving anamorelin had a LBM increase of at least 1 kg compared to less than 30% of placebo-treated patients (53% vs. 29%). The difference was even wider in patients with BMI < 20 kg/m^2 at baseline (57% vs. 22%): being that the baseline LBM value was lower in these patients, an absolute increase of at least 1 kg represents an even tougher goal.

The ROMANA pooled analysis showed that an increase of at least 1 kg of LBM at the End of Study was associated with a statistically significant increase of both FAACT A/CS and FACIT Fatigue score; the difference in these questionnaires' scores approximated 3.5 points on average, which is in line with the accepted minimum important difference (MID) for both parameters.

Hand Grip Strength

The CHMP Scientific Advice provided to the applicant had highlighted concerns regarding the clinical value of the HGS measurement.

At baseline there was a clear correlation between the dominant arm lean mass and the corresponding HGS ($r=0.66$; $P<0.001$) in all patients. However, at the end of the 12-week intervention, although arm lean mass changed, there was no correlation with change in HGS.

Magnitude of Body weight increase

In the pooled analysis of the two Phase 3 studies, the mean treatment effect at EOS (12 weeks or last observation carried forward [LOCF] since Week 6) for body weight was 2.2 kg. The magnitude of the effect size was as expected and fully in line with data reported in the Phase 2b study ST-ANAM-207. Importantly mean treatment effect for body weight was even higher and exceeded 3 kg in patients with BMI lower than 20 kg/m^2 at baseline.

Relevance of Anamorelin Effect on Fat Mass

In the ROMANA trials, anamorelin treatment significantly increased FM in both trials, with a treatment effect of 1 kg. Among patients with low BMI at baseline, fat mass increased by 1.7 kg.

Overall, the observed improvements in FM in anamorelin-treated patients, coupled with improvements in lean mass and ultimately body weight, can be interpreted as effect of anamorelin on food intake enhancement.

Effect of anamorelin on PROs

For the scope of clarity, and for better understanding of the emerging relevance of the PRO data, the Applicant would like to reiterate that two (and not eight) QoL instruments were administered in the Phase 3 studies. The two instruments were the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire. The Applicant provided information on completeness of FACIT-F and FAACT questionnaires already in the CSR provided at the time of MAA submission, per treatment and visit including data on the expected and received number of questionnaires at each visit and per arm. The ratio was always higher than 98%. As already mentioned, the Applicant cannot disagree that a pre-defined strategy to control for multiple testing in respect to QoL endpoints was not included in the

statistical analysis of both HT-ANAM-301 and HT-ANAM-302 trials. As such, from a methodological point of view, the analysis of these patient-reported outcomes should be regarded as exploratory in nature.

FAACT A/CS

Ribaudo et al tested validity by examining the relationship between A/CS scores and performance status (Ribaudo et al. 2001). Differences in A/CS scores were consistent with the premise that patients with more anorexia symptoms and concerns would also have poorer performance status ($p<0.05$), evidence of known-groups validity. Using baseline values for the sample and distribution-based methods, a change or difference of >3 to 4 points on the 48-point scale of the 12-item A/CS is considered meaningful (Ribaudo et al. 2001).

As a conservative approach, a MID of 4 points was applied to the responders pooled analyses of the HT-ANAM-301 and HT-ANAM-302 data. At EOS, the response rate in the overall population was significantly higher in the anamorelin group (50%) than in the placebo group (37%) ($p<0.001$).

Following a specific CHMP request, the proportion of responders among subjects alive at Week 12 was also computed by the control based pattern mixture model algorithm after applying incremental cut-offs for responder definitions ranging from a minimum of 1 point to a maximum of 5 of the FAACT A/CS score changes. Independently from the applied response cut-off, the proportion of responders was consistently and statistically significant higher in the anamorelin group (**Table 39**).

Table 39. Responders Analysis FAACT A/CS Study HT-ANAM-301, Study HT-ANAM-302 studies combined (PPM analysis)

	Placebo		**Anamorelin**			
ID Cut-off response	N	Proportion (95% CL)	N	Proportion (95% CL)	Difference Anamorelin-Placebo Mean (95% CL)	P-value
1	315	0.44 (0.38, 0.49)	639	0.52 (0.48, 0.56)	0.08 (0.02, 0.15)	0.0152
2	315	0.37 (0.32, 0.43)	639	0.46 (0.42, 0.50)	0.09 (0.02, 0.16)	0.0099
3	315	0.31 (0.26, 0.37)	639	0.40 (0.36, 0.44)	0.09 (0.02, 0.15)	0.0076
4	315	0.27 (0.22, 0.32)	639	0.36 (0.32, 0.39)	0.09 (0.03, 0.15)	0.0051
5	315	0.22 (0.17, 0.27)	639	0.31 (0.27, 0.35)	0.09 (0.03, 0.15)	0.0029

The treatment effect was positive (i.e. mean value above zero) for all the 12 FAACT A/CS items, although the magnitude of the effect varied among them. The three items with the highest treatment effect were ACT4 (“I am concerned about how thin I look”), ACT2 (“I am worried about my weight”) and ACT9 (Family/Friends are pressuring me to eat).

FACIT-F fatigue

The fatigue-related endpoints in the Phase 3 trial were initially selected due to trending benefits in fatigue observed in the Phase 2 studies using a variety of PROs. Furthermore, a previous definition of cancer cachexia (Evans *et al.* 2008) included the presence of fatigue as part of the diagnostic criteria.

Fatigue symptoms and concerns are considered more distal than anorexia/cachexia with respect to the mechanism of action of anamorelin.

When the 13 items of the Fatigue subdomain were examined individually, in no cases the effect size was significant. Changes from baseline to EOS of individual items of the FACIT-F Fatigue domain are displayed, in the overall population and by BMI at baseline.

The absence of a clear effect of anamorelin on the fatigue scores in the overall study population may be explained by the multifactorial aetiology and clinical complexity of cancer related fatigue.

CHMP Ground #2

- Restricting the indication to the subgroup with Body Mass Index < 20 kg/m^2 is not considered acceptable given that this subgroup was prioritised post-hoc and confirmatory conclusions of the benefit -risk based on this subgroup analyses cannot be made.

Summary of the Applicant`s position:

Data from the pooled analysis of the Phase 3 studies have clearly shown how the presence of BMI <20 kg/m^2 allows to enrich the target population by identifying a malnourished population with an advanced and rapidly progressing disease

At baseline of ROMANA patients with BMI <20 kg/m^2 had a more advanced disease as shown by worse performance status, more frequent history of weight loss >10% and presence of systemic inflammation.

Anamorelin effect was statistically significant for all body composition parameters in the overall population: treatment effect size was notably larger in patients with low BMI at baseline. This enhancement of treatment effect was not only due to larger increases in anamorelin-treated patients, but also to a more evident deterioration in the placebo arm.

In patients with low BMI, the mean FAACT A/CS score was lower at baseline in both arms. While FAACT A/CS score increased in the placebo group in patients with normal BMI, it remained unchanged in those with low BMI. Among anamorelin patients, FAACT A/CS increase was on average as twice as much (and as a result anamorelin treatment effect was 5-fold higher) in the low BMI group. The mean difference was 5.27 points, exceeding the MID of 4 points.

FACIT-F Fatigue domain score decreased marginally in patients with normal BMI in both treatment arms; on the contrary, in placebo patients with low BMI a substantial worsening of the Fatigue domain score was observed, contrasted and reversed by a small increase in the anamorelin arm, resulting in a statistically significant mean treatment effect of approximately +4 points.

Table 40. Changes from Baseline to End of Study in Body Composition parameters and Patient-Reported Outcomes overall and by BMI inclusion criterion– mITT Set Pooled HT-ANAM-301 and HT-ANAM-302

	Placebo			Anamorelin			Difference		Nominal
	N	Matching Baseline	Change From Baseline	N	Matching Baseline	Change From Baseline	Point Estimate	95% CI	p-value
Total Body Mass									
All patients	256	65.95 (13.71)	-0.71 (4.01)	520	66.98 (13.13)	1.79 (4.55)	2.50 (4.38)	1.84, 3.16	<.001
BMI < 20 kg/m^2	64	51.95 (8.28)	-0.93 (3.19)	103	52.02 (7.05)	2.44 (4.77)	3.37 (4.24)	2.04, 4.70	<.001
BMI ≥ 20 kg/m^2	192	70.62 (11.87)	-0.64 (4.26)	417	70.68 (11.57)	1.63 (4.49)	2.26 (4.42)	1.51, 3.02	<.001
Total Lean Mass									
All patients	256	45.12 (8.61)	-0.37 (2.69)	520	45.5 (7.97)	1.16 (2.71)	1.52 (2.71)	1.12, 1.93	<.001
BMI < 20 kg/m^2	64	39.54 (6.79)	-0.46 (2.59)	103	40.13 (6.67)	1.25 (2.66)	1.71 (2.64)	0.88, 2.54	<.001
BMI ≥ 20 kg/m^2	192	46.98 (8.36)	-0.34 (2.73)	417	46.83 (7.71)	1.13 (2.73)	1.47 (2.73)	1.00, 1.94	<.001
Appendicular LBM									
All patients	256	19.15 (4.35)	-0.19 (1.59)	520	19.39 (4.17)	0.56 (1.69)	0.75 (1.66)	0.50, 1.00	<.001
BMI < 20 kg/m^2	64	16.15 (3.39)	-0.31 (1.71)	103	16.39 (3.38)	0.66 (1.69)	0.97 (1.70)	0.43, 1.50	<.001
BMI ≥ 20 kg/m^2	192	20.15 (4.18)	-0.15 (1.55)	417	20.13 (4.02)	0.54 (1.69)	0.68 (1.65)	0.40, 0.96	<.001
Fat Mass									
All patients	256	18.38 (7.75)	-0.33 (2.63)	520	19 (8.07)	0.65 (2.87)	0.97 (2.79)	0.55, 1.39	<.001
BMI < 20 kg/m^2	64	10.26 (3.46)	-0.46 (1.7)	103	9.74 (3.33)	1.2 (2.96)	1.66 (2.55)	0.86, 2.46	<.001
BMI ≥ 20 kg/m^2	192	21.08 (6.84)	-0.28 (2.88)	417	21.28 (7.22)	0.51 (2.84)	0.79 (2.85)	0.30, 1.28	0.002
FAACT A/CS Domain Score									
All patients	270	30.02 (8.46)	1.59 (9.11)	539	29.6 (8.3)	3.43 (9.15)	1.84 (9.14)	0.50, 3.18	0.007
BMI < 20 kg/m^2	64	27.77 (8.02)	0.45 (10.46)	109	25.48 (8.39)	5.73 (9.99)	5.27 (10.16)	2.11, 8.43	0.001
BMI ≥ 20 kg/m^2	206	30.71 (8.48)	1.95 (8.65)	430	30.64 (7.96)	2.85 (8.85)	0.91 (8.79)	-0.56, 2.37	0.224
FACIT-F Fatigue Domain Score									
All patients	267	30.74 (10.65)	-0.91 (10.39)	535	30.46 (10.39)	-0.35 (9.93)	0.56 (10.09)	-0.92, 2.05	0.455
BMI < 20 kg/m^2	63	30.25 (11.06)	-3.22 (10.62)	109	27.74 (11.69)	0.72 (10.94)	3.94 (10.82)	0.56, 7.32	0.023
BMI ≥ 20 kg/m^2	204	30.89 (10.55)	-0.2 (10.24)	426	31.15 (9.93)	-0.62 (9.66)	-0.42 (9.85)	-2.07, 1.23	0.616

To support the concept of a more favourable risk/benefit ratio in the BMI < 20 kg/m^2 population at baseline, an analysis has been conducted evaluating the frequency of TEAEs by treatment arm and BMI category. The incidence of TEAEs is comparable between the two populations, and to the overall ROMANA population. Similarly, comparison of TEAE frequency between treatment arms of each BMI population yields similar ratios, providing initial reassurance as to the lack of an increased risk by anamorelin treatment in low BMI patients. Importantly, the incidence of hyperglycaemia, liver transaminases increases, cardiac disorders and oedema was comparable between treatments.

The magnitude of the effect size was as expected and fully in line with data reported in the Phase 2b study ST-ANAM-207. Importantly mean treatment effect for body weight was even higher and exceeded 3 kg in patients with BMI lower than 20 kg/m^2 at baseline.

In terms of percent change from baseline, the mean weight gain in patients with low BMI was higher than 5%. This is a clinically relevant threshold when considering that unintended weight loss of at least 5% represents one of the diagnostic criteria of cancer cachexia, and that increases of at least 5% have been shown to be associated with improved outcomes (Patel et al. 2016). The proportion of patients achieving ≥5% increase in body weight following anamorelin treatment was 34.1% in the overall efficacy population and 47.3% among those with BMI < 20 kg/m^2 at baseline (Currow et al. 2017) compared with 13.4% and 17.4% in the placebo arm, respectively.

As a conservative approach, an MID of 4 points was applied to the responders pooled analyses of the HT-ANAM-301 and HT-ANAM-302 data. At EOS, the response rate in the overall population was significantly higher in the anamorelin group (50%) than in the placebo group (37%) (p<0.001).

Among patients enrolled with BMI <20 kg/m^2 at baseline the response rate in the anamorelin arm rose to 59%, whilst decreasing to 33% in the placebo arm.

In patients with BMI < 20 kg/m^2 at baseline, increases of the Fatigue subdomain were larger in the positive direction in the anamorelin arm, and decreases were wider in the placebo group. The difference between the two arms was therefore broader and treatment effect size of anamorelin improved markedly throughout all items.

CHMP Ground #3

- There are significant concerns regarding evaluation of the safety profile of anamorelin based on the overall small size of the clinical safety database, and in particular in light of the conclusion from the GCP inspection that the integrity of the safety database is compromised. The trends of higher morbidity and on treatment mortality rates across the clinical studies and the signals for cardiovascular events and hepatotoxicity observed in pre-clinical studies with limited safety margins in relation to the doses used in human studies cannot be comprehensively evaluated.

Summary of the Applicant`s position:

The Scientific Advice sought by the applicant included a number of Clinical Questions on the adequateness of safety assessments, which were all positively evaluated by the Scientific Advice Working Party (SAWP). In particular, the SAWP confirmed the adequateness of the proposed safety database for the assessment of benefit-risk in view of a Marketing Authorization, endorsing the Applicant's rationale in support of the adequateness of anamorelin safety profile characterization specifically "in terms of number of individuals in the global registration program".

The safety experience from the dose ranging Phase 2 study ST-ANAM-207 in patients with advanced NSCLC had shown a safety profile in line with what could be expected from either the underlying disease (fatigue and asthenia, dyspnoea and cough) or chemotherapy toxicity (blood cytopenias and alopecia). Other unexpected serious events had not been identified, neither in previous Phase 1 and 2 studies with anamorelin nor in other studies with ghrelin agonists in general. Therefore it was not considered necessary to further increase the sample size of the two confirmatory studies, which were well powered for rejecting the null hypothesis of the two co-primary efficacy endpoints considering the HGS effect size assumptions.

The Applicant has reiterated that drug-relatedness assessment of TEAEs was attributed by the Investigator only in accordance with the regulations in force for the conduct of clinical studies. The drug relatedness analysis presented in the Integrated Summary of Safety and summarized in the Clinical Overview of the initial submission of this application was based solely on the Investigator's assessment. In the integrated safety analysis, if the relationship of AE was reported as "unknown" or "non-assessable" by the Investigator, it was conservatively regarded as "related".

The evaluation of the cases with SAEs was provided also by the applicant as "Company comment" in the pertinent narratives appended to each Clinical Study Report, including causality assessment in compliance with the Clinical Trials Directive 2001/20/EC Article 7.3.2 Causality Assessment. As mentioned above, however, such "Company comment" has not been used for Summary analyses.

During the course of the review, the assessment reports have hinted that an excess mortality was noted with anamorelin in the Phase 3 programme. This topic was discussed in detail at the Oral Explanation meeting.

Extensive *in vitro* research has investigated the potential role of ghrelin in carcinogenesis and cancer progression, possibly via an autocrine/paracrine pathway. Endogenous ghrelin stimulates release of

GH, which regulates IGF1 concentrations. IGF1 has mitogenic and anti-apoptotic properties and IGF1 levels has been positively correlated with modestly increased risk of proliferation of several cancers. Moreover, large, long-term registries of GH therapy could not demonstrate an increased risk of neoplasms or recurrent tumours in paediatric patients or in adults nor could such a relation be refuted.

The Applicant cannot agree with the CHMP statement that there is a trend in the overall survival data showing that survival is lower in the Anamorelin group when compared to placebo, as it is simply unacceptable to believe that a 0.27 months (e.g. approximately 8 days or about 3% of the expected life expectancy)) difference has any meaningful clinical relevance in this patient population.

The CHMP's Assessment Report at Day 180 quoted that the median survival time over 1 year was 11.27 months for the placebo group and 10.13 months for the anamorelin group. This data refers only to the subgroup analysis of patients with ECOG 0-1 at baseline. However, the same subgroup analysis shows that in patients with ECOG 2, the median survival time over 1 year was 4.83 months for the placebo group and 5.70 months for the anamorelin group. There is no reason to believe, and it would be counterintuitive, that anamorelin may increase mortality in patients with better performance status while improving survival in those with worse performance status.

The survival rates at 3 months from enrolment were 82.7% with anamorelin and 81.5% with placebo, at 6 months survival rates was 66.1% and 63.2% for anamorelin and placebo, respectively. In both ECOG subgroups (0-1 and 2) the Kaplan Meier estimate of patients alive at 3 months and at 6 months was in favour of anamorelin. In summary, the data clearly indicate that anamorelin does not induce excess mortality.

A very similar proportion of patients enrolled in the HT-ANAM-301 and 302 studies experienced TEAEs leading to death in the anamorelin and in the placebo arms (16.2% vs. 15.5% respectively). When TEAEs were analysed at SOC level, there was no sign of a cluster of events leading to an incremental risk of death in the anamorelin arm, including for cardiac disorders. Of note, the frequency of TEAEs in the SOC Cardiac disorders leading to death was 0.5% with anamorelin and 1.2% with placebo.

Similarly, the frequency of all Serious TEAEs was 27% in both the anamorelin and the placebo arm; the frequency of Serious TEAEs in the SOC Cardiac disorders was lower with anamorelin (1.5%) than with placebo (2.5%). Likewise the frequency of TEAEs leading to discontinuation in the SOC Cardiac disorders was 0.5% with anamorelin and 1.2% with placebo.

When only adverse events of special interest (AESI) were considered, the frequency of Serious AESI was comparable in the two arms as they were reported in 20 (3.1%) patients receiving anamorelin and in eight patients (2.5%) randomized to placebo. Of note, Serious AESI were assessed as drug-related by the investigator in only 3 patients (0.5%) receiving anamorelin

Hepatic toxicity

Table 41 displays in the consistent cohort of patients who entered the extension study HT-ANAM-303, the incidence of the TEAEs with PT of Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Blood Alkaline Phosphatase Increased, Blood Bilirubin Increased or Gamma Glutamyl-Transferase increased reported in Studies HT-ANAM-301 and HT-ANAM-302 and in the extension study. The incidence of all events decreased during the extension phase with no signs of accumulated toxicity as a consequence of prolonged exposure. Overall these data are further reassuring and suggest that the risk of drug-induced liver injury with anamorelin is negligible, if any.

Table 41. Frequency of TEAEs of increased laboratory liver panel in pivotal studies in cohort of patients who completed the studies HT-ANAM-301 and HT-ANAM-302 and entered the extension study HT-ANAM-303

	Placebo (N=167)				**Anamorelin (N=343)**			
	HT-ANAM 301/302		**HT-ANAM 303**		**HT-ANAM 301/302**		**HT-ANAM 303**	
Increase of	n	%	n	%	n	%	n	%
ALT	12	7.2%	1	0.6%	28	8.2%	10	2.9%
AST	13	7.8%	2	1.2%	21	6.1%	9	2.6%
Alkaline Phosphatase	9	5.4%	1	0.6%	19	5.5%	8	2.3%
Total Bilirubin	2	1.2%	0	-	0	-	0	--
Gamma Glutamyl-Transferase	2	1.2%	1	0.6%	2	0.6%	3	0.9%

Cardiac Toxicity

Anamorelin does not affect ventricular repolarization even at the supra-therapeutic dose of 300mg daily. It induces spurious prolongation of the QTcF interval because of the widening of the QRS interval.

The results from the thorough QT study have conclusively excluded any clinically relevant effect of anamorelin on cardiac repolarization (JTc interval) not only at the intended therapeutic dose of 100mg but also at the supra-therapeutic dose of 300mg. The mean QTcF interval almost equals mean QRS interval plus mean JTc interval, thus confirming that effect of anamorelin on QTcF interval is principally due to the effect of the drug on the QRS interval. There were no events of torsade de pointes in the entire anamorelin development.

In the two pivotal studies (HT-ANAM-301 and HT-ANAM-302), there was one case of AV block in the anamorelin 100mg groups compared to none in the placebo groups.

The unbound free fraction is approximately 0.07µM. The safety margin for the block of either of the two types of sodium current is of the order of several magnitudes. This suggests that at the therapeutic concentrations, anamorelin is not potent enough a sodium channel blocker to unmask concealed Brugada syndrome or induce this syndrome.

In the Phase 3 studies, the incidence of deaths due to treatment emergent cardiac events was 4-fold higher on placebo (1.2%) than on anamorelin (0.3%).

Report from the SAG

Following the receipt of the detailed grounds for the re-examination, and at the request of the applicant the CHMP convened an Oncology SAG on Adlumiz inviting the experts to provide Responses to a List of Questions, and in addition their comments on the Grounds for negative opinion, taking into account the grounds for re-examination submitted.

Overall, the SAG agreed on most grounds for negative opinion, namely that a clinically relevant effect has not been established in the overall population or in the subgroup with Body Mass Index (BMI) < 20 kg/m^2, and that in the absence of sufficient efficacy, the benefit risk balance cannot be considered positive (see answer to question No. 1).

The SAG did not have major concerns on the small differences observed in adverse events or survival between treatment groups, which were too small to be of significance. However, remaining uncertainties about the safety profile due to non-clinical findings and possible underreporting would need to be addressed (see answer to question No. 3).

1. **What is the view of the SAG on the clinical relevance and robustness of the observed differences in lean body mass compared to baseline and to placebo in the total population and in the post-hoc defined subgroup of patients with a lean body mass <20 kg/m^2, also taking into account the effects on QoL and other secondary endpoints related to a beneficial clinical outcome.**

The effects of anamorelin HCl on lean body mass (LBM) and muscle strength were assessed in two placebo-controlled randomized controlled trials (301 and 302). In both trials, LBM was assessed using dual energy x-ray absorptiometry (DEXA), which is a standard method with acceptable validity. Muscle strength was measured by handgrip strength (HGS) of the non-dominant hand using a grip strength testing device.

The primary efficacy analyses were to compare the anamorelin group to the placebo group on these two co-primary endpoints in the ITT population (all randomized patients) using a ranking algorithm determined on the basis of both the change from baseline to the average at 6 and 12 weeks in the primary endpoints, and by the survival status. Missing measurements were handled using multiple imputation. The anamorelin group was to be claimed to be superior only if both co-primary efficacy tests (LBM and HGS) were rejected in favour of the anamorelin group based on the P-values obtained from Wilcoxon rank-sum tests (5% level, two-sided). There was no plan to control for the overall alpha for the secondary efficacy analyses.

Both trials failed to show a statistically significant difference for the co-primary endpoint HGS (P-value 0.1475 and 0.6480 for trials 301 and 302, respectively), so that formally, the anamorelin group could not be concluded superior to the placebo group in any of the two trials.

The applicant company claimed that efficacy can be concluded on the basis of a consistent statistically significant difference in terms of LBM (P-value < 0.0001 in both trials). For LBM, the median change from baseline over 12 weeks (the average of the change from baseline at Week 6 and the change from baseline at Week 12) was -0.47 (95% CI: -1.00, 0.21) v. 0.99 (0.61, 1.36) in trial 301 and -0.98 (-1.49, -0.41) v. 0.65 (0.38, 0.91) in trial 302, for the amorelin v. placebo group, respectively. The treatment difference between groups was 1.46 kg and 1.63 kg for trials 301 and 3012, respectively. In the subgroup of patients with BMI < 20 kg/m^2, the difference in total body mass was 3.47 kg (1.84, 5.09).

The SAG acknowledged that a consistently small numeric improvement was observed for LBM, in secondary analyses in the context of non-statistically significant primary analyses of the two trials. However, the effect in terms of LBM was very small in absolute and relative terms considering the substantial weight loss experienced by many patients.

There are no data from the trials presented or other studies to allow quantification of an association between changes in LBM of the magnitude demonstrated in these trials and functional improvement, improvement in quality of life, specific symptom benefit or a positive impact on performance status. Such small differences as those presented would not anyway be expected to be associated with a tangible clinical benefit experienced by patients or result in any changes in clinical management. Indeed, the increase in LBM was not associated with an increase of grip strength.

The estimated effect size might furthermore depend strongly on some of the assumptions used in the analysis as sensitivity analyses have shown a decrease of the already small observed effect.

Although some outcomes appeared to be numerically improved on the basis of exploratory or subgroup analyses (e.g., BMI < 20 kg/m^2), it is difficult to conclude on the clinical significance of the findings due to lack of internal consistency and post hoc analyses without a predefined handling of multiplicity.

In conclusion, based on the co-primary and all the secondary analyses and argumentations presented, a clinically relevant effect has not been established.

2. **What is the view of the SAG on the reported efficacy on lean body mass of anamorelin added to concomitant (gluco)corticosteroid treatment, taking into account the differences in individual study data.**

It is difficult to comment on the possible effects on lean body mass of anamorelin added to concomitant (gluco)corticosteroid treatment and if steroids could have contributed to some of the observation of increase in LBM, although corticosteroids are expected to negatively affect LBM. Unfortunately, the dosing and duration of steroid exposure in the trials is unclear. However, given the blinded randomized design, bias due to unequal concomitant administration is considered unlikely.

There may be toxicity associated with concomitant administration, e.g., the observed increase in blood glucose associated with anamorelin that could also be explained by growth hormone or related mechanism of action and would in any case be manageable. No fluid retention was observed.

3. **What is the view of the SAG on the overall safety of anamorelin and their relevance in the target population given the frailty of the patients for which anamorelin is intended to be used, taking into consideration the consistently observed reduction of median overall survival and survival rate in the anamorelin arm compared with placebo and for instance the findings of the (preclinical) cardiotoxicity and hepatotoxicity.**

Anamorelin was associated with slight increased toxicity in terms of treatment-emergent adverse events (78% vs. 73.6%) and serious adverse events (27.4% vs. 26.7%) compared to placebo. Overall it is difficult to conclude on the clinical significance of such differences. Similarly, small differences of the survival curves (HR=1.06; 95% CI: 0.89, 1.26) are unlikely to represent a real effect.

Some underreporting of toxicity seems possible in view of the low frequency of adverse events reported for patients receiving concomitant chemotherapy but this may be due to causality adjudication and in any case should be similar across study groups.

Concerning cardiotoxicity and the non-clinical findings, clinical data do not confirm a concern but it is unclear to what extent underreporting or concomitant medications could have influenced the findings. Existing uncertainties would need to be further addressed, e.g., with continuous cardiac monitoring in a suitable clinical setting.

In conclusion, there were no major safety concerns but some uncertainties remain.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the SAG.

Ground#1. Clinical relevance of observed effects on LBM, functional outcomes and Quality of Life measures

In the scientific advice received in 2012 , the CHMP had expressed significant concerns about the clinical significance of the co-primary endpoints of ‘change in LBM’ and ‘change in HGS’. At the time

CHMP had recommended that “demonstration of a clear effect on one objective variable reliably measuring anabolic drug activity combined with one adequately validated subjective variable ensuring patient relevance”, which is e.g. ‘change in LBM’ in combination with a well-established and validated QoL endpoint. This advice was not taken into consideration in the already ongoing pivotal studies.

The definition and validation of the MID for the LBM and both established and validated QoL (FAACT A/CS and FACIT-F fatigue) is unclear in the applied indication, and was not supported by the literature references provided by the applicant. The clinical relevance for the definition of the MID is lacking.

LBM

The Applicant argued that recent interventional studies in NSCLC patients have also provided evidence that LBM increases of ≥ 1 kg are clinically meaningful based on longer survival compared to patients who do not gain at least 1 kg of LBM (Crawford *et al.*, 2014). According to the applicant pooled data from the two Phase 3 pivotal studies show that more than 50% of patients receiving anamorelin had a LBM increase of at least 1 kg compared to less than 30% of placebo-treated patients (53% vs. 29%). The difference was even wider in patients with BMI < 20 kg/m^2 at baseline (57% vs. 22%), and as the baseline LBM value was lower in these patients, an absolute increase of at least 1 kg represents an even tougher goal. If the above argumentation was correct, then supportive results would have been expected from the OS analysis, which however favoured the placebo treated patients. Furthermore, an additional post-hoc “cut-off” point for BMI would not have been required. Importantly, both studies failed to show a positive effect on the co-primary endpoint.

The difference of median changes between placebo and anamorelin was 1.46 kg in Study HT-ANAM-301 and 1.63 kg in Study HT-ANAM-302 and was highly statistically significant ($p < 0.0001$) in both studies. Median increase from baseline in LBM in ROMANA-1 0·99 kg [95% CI 0·61 to 1·36] in the anamorelin vs. -0·47 kg [-1·00 to 0·21] in the placebo group) and ROMANA 2 (0·65 kg [0·38 to 0·91] vs. -0·98 kg [-1·49 to -0·41], respectively). Based on the applicants defined MID of 1 kg it should be concluded that most patients did not experience a MID. The mean difference with placebo however reached the MID and therefore can be concluded that anamorelin slows down the deterioration caused by the underlying condition.

Regarding the impact of concomitant corticosteroid use, the applicant was requested during the initial assessment to perform a post-hoc analysis, stratifying for concomitant corticosteroid use. The results of the post-hoc analysis are discussed below.

It should be noted that the patients included in the analyses was a heterogeneous population with different cancer stages and tumour histology (**Table 42**).

Table 42. Changes of LBM over 12 weeks in patients receiving/not receiving corticosteroids at any time during the study.

		Baseline			Change from Baseline over 12 weeks				
	N	Median	alive	dead	N	Median	95%CI	Median difference	95%CI
HT-ANAM-301							95%CI		
No Concomitant use of Corticosteroids									
Anamorelin HCl	56	43.85	42	14	56	0.33	(-0.85, 1.08)	0.25	(-1.67, 2.13)
Placebo	22	39.49	18	4	22	-0.09	(-2.19, 0.86)		
Concomitant use of Corticosteroids									
Anamorelin HCl	255	46.91	219	37	256	1.09	(0.68, 1.49	1.65	(0.94, 2.38)
Placebo	130	46.88	107	24	131	-0.52	(-1.14, 0.14		
HT-ANAM-302									
No Concomitant use of Corticosteroids									
Anamorelin HCl	132	43.39	108	24	132	0.63	(0.17, 1.13)	1.95	(0.93, 3.12)
Placebo	66	42.67	50	16	66	-1.53	(-2.72, -0.47)		
Concomitant use of Corticosteroids									
Anamorelin HCl	177	44.01	151	27	178	0.69	(0.12, 0.99)	1.35	(0.63, 2.07)
Placebo	87	45.05	79	9	88	-0.76	(-1.06, 0.02)		

It is assumed that corticosteroid treatment may have an effect on weight gain. Inconsistent and inconclusive results across the two pivotal studies were rereported in terms of differences in LBM changes between treatment groups with and without concomitant treatment with corticosteroids.

Overall, the interpretation of the applicant's data is difficult and a potential confounding effect of corticosteroids cannot be evaluated.

HGS

The hand grip strength failed to demonstrate a statistically significant improvement with anamorelin compared with placebo. As already concluded the pivotal should be considered failed as one of the co-primary endpoints did not demonstrate a statistically significant change.

PRO

From a methodological point of view, the analysis of these patient-reported outcomes should be regarded as exploratory in nature.

FAACT A/CS

As a conservative approach, a MID of 4 points was applied to the responders pooled analyses of the HT-ANAM-301 and HT-ANAM-302 data. At EOS, the response rate in the overall population was significantly higher in the anamorelin group (50%) than in the placebo group (37%) ($p<0.001$). These results should be interpreted with some caution for the clinical relevance of the MID remains to be established.

FACIT-F fatigue

When the 13 items of the Fatigue subdomain were examined individually, in no cases the effect size was significant.

In conclusion, as already discussed and concluded the magnitude of the claimed superiority of anamorelin vs. placebo in few of the endpoints analysed is considered marginal and the clinical relevance of the various observations remains to be established. The lack of consistency of results regarding co-primary and secondary endpoints raised serious concerns over the claimed activity of the drug.

In the response to the re-examination the applicant submitted an additional responder analysis based on post-hoc defined MID. The post-hoc analysis indicated a small difference between active and placebp in patients reacheding the MID for LBM. . The mean difference compared to placebo however did reach the MID suggesting a slower deterioration. These results should be interpreted with caution as the additional MID analysis is hampered by a lack of justification for the used MID.

Ground#2. Post-hoc prioritisation of sub-group with Body Mass Index < 20 kg/m^2

As detailed in the assessment of the intial evaluation, a post-hoc subgroup analysis in patients with BMI lower than 20 kg/m^2 at baseline showed a mean treatment effect for body weight exceeding 3 kg.

The selection of this cut-off point came after the finalisation of the trials. Notably in the initial MAA submission, the applicant did predefine a BMI cut-off of <>18.5 kg/m^2 which failed for the change from baseline over 12 weeks in LBM (**Table 43**).

Table 43. Analysis of Change in Lean Body Mass (kg) from Baseline Over 12 Weeks Intent-to-Treat Population By BMI (a pooled analysis has not been not reported).

		HT-ANAM-301		HT-ANAM-302	
		Placebo	**Anamorelin**	**Placebo**	**Anamorelin**
	Statistic				
BMI <= 18,5		**(N=15)**	**(N=30)**	**(N=25)**	**(N=49)**
Without Normality Baseline [1]	Median	37.70	39.12	38,61	37,11
Change from BaselineOver 12 Weeks [2]	Median (95% CI)	-1.302 (56*,0.659)	0.585 (-1.412, 2.060)	-0,933 (-3,034, 0,199)	-0,273 (67*,1,159)
	P-value		0.0661		0,6035

[1] Baseline is defined as the last value obtained prior to the first dose of study drug.

[2] Change from baseline over 12 Weeks is defined as the average of the change from baseline at Week 6 and the change from baseline at Week 12.

Notable is the large shift in the level of statistical significance in the pooled analysis group < 20 kg/m^2 after the adaptation of the cut-off value (<> 18.5 to <> 20 kg/m^2) when the individual studies are pooled suggesting a lack of robustness in the data.

A post-hoc pooled analysis of failed individual studies cannot be considered as a proof of evidence for efficacy. From a methodological point of view, as this subgroup analysis was added post-hoc, a data driven approach in an overall negative study cannot be excluded. Therefore, the results in patients with BMI< 20 kg/m^2 can be considered only hypothesis generating and are not acceptable to draw confirmatory conclusion. Similarly to the overall population, the inconsistency of the results regarding primary and secondary endpoints observed in patients with BMI < 20 kg/m^2 does not allow to draw any definitive conclusion over the claimed activity of the drug in this subgroup of the population treated.

Ground #3-Limitations in ability to evaluate safety concerns

From the overview of AEs from the total Safety Population of the pivotal phase III trials there appears to be a trend of increase in TEAEs, Drug Related TEAEs, any chemotherapy related TEAE, TEAE leading to Deaths and SAES for Anamorelin 100 mg group compared to the placebo group. If the safety population is limited to studies RC-1291-203/205, RC-1291-206, ST-ANAM-207, HT-ANAM-301, and HT-ANAM-302 for all cancer patients, similar results were observed. In addition, in some cases the

trend was even higher in the anamorelin 50 mg group compared to anamorelin 100 mg group e.g. TEAEs and SAEs.

An additional safety set was defined to characterise the long term safety of anamorelin. This included 343 patients who received anamorelin HCl 100 mg during the two pivotal trials and participated in the additional 12 week extension study HT-NAM-303. The results suggest that with an additional 12 weeks of exposure, the overall frequency of TEAEs was lower compared to the original studies, which leads to an inexplicable lack of consistency. The frequency of TEAEs of special interest was comparable between anamorelin HCl 100 mg and placebo groups, with 14.6% vs. 12.6% respectively. Higher frequencies of TEAEs were seen for the event category of Hepatic Disorders (6.4 % vs. 3.6%) and Blood Glucose Increase (5.5% vs. 3.6%).

Survival

It should be noted that both pivotal studies were not designed to primarily assess any difference in mortality with anamorelin vs. placebo and NSCLC stage, ECOG status, tumour histology or disease duration were not included as stratification factors at randomization. Over the 12-month follow-up time in the pivotal studies, the percentage of subject deaths was 58.0% in the placebo group and 60.2% in the anamorelin group. Median survival time over 1 year was 9.2 months for the placebo group and 8.9 months for the anamorelin group. The hazard ratio was slightly increased for anamorelin vs. placebo; HR 1.06 (p = 0.4691).

Although a difference in death rates between the two treatment groups was observed during active treatment it cannot be concluded that anamorelin does suggest explicitly a detrimental effect on the survival rate while patients are on treatment. It should be noted that patients received treatment for 12 weeks in study 301 and 302 and an additional 12 weeks in study 303. When patients were off treatment after 6 months , patients in the anamorelin group t seem to have a higher mortality rate.

As already discussed in the assessment of the applicant responses mortality and overall survival in the target population is nearly exclusively dominated by the underlying cancer disease and, as anamorelin had no beneficial effect on the disease outcome, the absence of significant differences in overall mortality can be expected. In this setting any impact on mortality for an investigational drug could be expected only if it was associated with a dramatic toxicity. But this is clearly not the case for anamorelin, in particular, taking into account the short treatment period of 12 weeks.

Given the potential arrhythmia effect of anamorelin (see below) it cannot be excluded that the slightly higher overall observed death rate, which suggests to emerge when on treatment, could be contributed to the (cardiac) toxicity of the active substance. As anamorelin may potentially be administered for a longer period of time than the 6 months in the studies it cannot be excluded that more deaths due to anamorelin treatment will occur. In order to definitely demonstrate whether anamorelin has no or marginal effect on sudden death or a higher death rate more research would be required.

Hepatic toxicity

Anamorelin showed ALT, AST, alkaline phosphatase and GGT increases, however no differences in hepatic damage were seen between active and placebo treated patients. The relatively limited safety database (less than 500 patients followed for about one year) cannot give reassurance over the hepatic safety concerns raised by the preclinical studies.

Cardiac toxicity

Anamorelin shows a significant arrhythmic potential due to targeting the Na^+channel and has a rather narrow therapeutic range which is characterized by a non- linear PK, sensitivity to CYP3A4 inhibition, other potential drug interactions and possibly hepatic dysfunction. The thorough QT study (HT-ANAM-112) confirmed that anamorelin is blocking cardiac sodium channels and the impact of this effect on potential arrhythmias was demonstrated.

The observations in the thorough QT study appear in conflict with the observations in ROMANA-1 and 2 databases. the incidence of TEAEs in the category "Cardiac arrhythmias SMQ" seem somewhat higher in the placebo group; 6.2% and 5.0 % in the placebogroup vs. 5.9 and 2.9 %, in the anamorelin group for studies 301 and 302 respectively; in The relatively short study duration and the limited number of patients treated hamper an adequate assessment. Further, cardiac arrhythmias adverse events may not be detected in these short studies with relatively limited patient numbers. Additional, adequate evaluation of arrhythmias would require measurement techniques like 24h hour monitoring (Holter ECG) and other methods to be detected.

Furthermore, based on the findings and the observations of the inspection at two sites, AEs were underreported in the clinical trials. The safety data reported were incomplete and thus the quality and accuracy of the data of the two trials was adversely affected, which could have a negative effect on the safety results presented.

In conclusion, taking into consideration the preclinical findings, the results of the thorough QT study, the flaws and uncertainties in the clinical assessment of a drug-relationship in the pivotal studies and the concerns of underreporting of adverse events, it cannot be concluded that anamorelin is not associated with cardiac toxicity. There are signals both from the pre-clinical and clinical studies which would merit further investigation in order to exclude the potential detrimental effects of anamorelin. Given that there are concerns about the accuracy of the safety data due to the GCP shortcomings, it is not possible at this stage to sufficiently characterize the safety profile of anamorelin or consider the appropriate means to minimize the risks associated with its use.

Third party intervention during the re-examination of Adlumiz

The Contract Research Organisation (CRO) for Helsinn Therapeutics that conducted a number of activities in the framework of the pivotal clinical trials for Adlumiz, submitted a document after the start of the re-examination procedure challenging the findings of the GCP inspection conducted during the initial evaluation of Adlumiz. In its intervention the CRO maintained that the safety data were recorded in compliance with the approved trial protocols and were thus in compliance with GCP.

The CHMP considered this intervention, as well as the inspectors' position on the CRO's intervention and concluded that the arguments put forward by the CRO regarding the relevant findings of the inspection reports did not impact the CHMP's conclusion that the safety data reported in the clinical study reports cannot be relied upon for assessment.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

See Section 3.1.1

6.1.2. Available therapies and unmet medical need

See Section 3.1.2

6.1.3. Main clinical studies

See Section 3.1.3

6.2. Favourable effects

In patients treated with anamorelin a median increase from baseline LBM of 0.99 kg in ROMANA-1 ([95% CI 0.61 to 1.36] vs -0.47 kg with placebo [-1.00 to 0.21], p<0.0001) and of 0.65 kg in ROMANA-2 study ([95% CI 0.38 to 0.91] vs -0.98 kg with placebo [-1.49 to -0.41], p<0.0001) was reported. The mean difference from placebo of LBM was 1.46 kg in ROMANA-1 and 1.63 kg in ROMANA-2 (p < 0.0001 for both studies) representing 3-4% of median baseline LBM in the pivotal trials.

The FAACT A/CS subscale, showed statistical superiority for anamorelin over placebo in the pivotal studies (LS mean [SE] 2.21 [0.617] and 2.14 [0.676] respectively).

A post-hoc responder analysis showing that more than 50% of patients receiving anamorelin had a LBM increase of at least 1 kg (defined MID) compared to less than 30% of placebo-treated patients (53% vs 29%) at the end of the study.

A newly submitted responder analysis based on a MID of 4 points in the FAACT A/CS score showed, at EOS, that the response rate in the overall population was significantly higher in the anamorelin group (50%) than in the placebo group (37%), (p<0.001).

A post-hoc subgroup analysis in patients with BMI lower than 20 kg/m^2 at baseline showed a mean treatment effect for body weight exceeding 3 kg. In the response to the ground for re-examination a responder analysis based on a MID of 1kg in patients with BMI < 20 kg/m^2 at baseline showed 57% responders in the anamorelin arm vs 22% in the placebo group. The mean difference in the FAACT A/CS was 5.27 points in favour of the active treated patients, exceeding the MID of 4 points. In placebo patients with low BMI a substantial worsening of the FACIT-F Fatigue domain score was observed, contrasted and reversed by a small increase in the anamorelin arm, resulting in a statistically significant mean treatment effect of approximately +4 points.

6.3. Uncertainties and limitations about favourable effects

During the scientific advice procedure for this product, the CHMP had highlighted concerns over the clinical relevance of the proposed co-primary endpoints for the target population.

The impact of missing data on the results presented is still unknown. The GCP inspection conducted in for this application revealed that concomitant medication – other than for tumour treatment – was not systematically collected. A potential impact of e.g. systemic corticosteroids on weight gain could therefore not be assessed.

As detailed in the initial evaluation of Adluimiz, the co-primary endpoint defined as change in lean body mass LBM and change in HGS failed to show a statistically significant improvement or any clinically benefit with anamorelin over placebo in both pivotal trials. As the co-primary endpoint was not met formally both studies should be considered as negative. Regarding the secondary QoL endpoints only an improvement in a few subscales was reported with anamorelin compared with placebo. However, this does not automatically translate into clinical benefit for the patients treated.

As already discussed previously the effect of the included secondary endpoint FAACT A/CS was (with the closely related FAACT SEA and the FAACT TOI[2]) the only statistically significant effect seen in the whole FAACT score. The FACIT-F and the other sub scores (FACIT SEF, FACIT-F TOI, FAACT total score, fatigue domain of the FACIT-F) did not show a statistically significant change.

In the response to the ground for re-examination no MID was defined prospectively; the MIDs were only discussed retrospectively. Further, the clinical relevance of the defined MID is unclear as the changes are not related to the patient reported benefit in the population under investigation.

For the interpretation of the newly submitted FAACT A/CS responder analysis as well as the LBM responder analysis, it needs to be taken into consideration that the method applied for analysis aims at estimation of the treatment effect that would have been observed if all patients had survived until EOS and all patients had been fully adherent to treatment, which could lead to overestimation of the benefit.

For the FACIT-F no MID was identified therefore no responder analysis was performed.

Regarding the claimed efficacy in patients with a BMI below 20 kg/m^2 it was already concluded that from a methodological point of view as this subgroup analysis was added post-hoc a data driven approach in an overall negative study cannot be excluded. Therefore, the results in patients with BMI< 20 kg/m^2 can be considered only hypothesis generating and are not acceptable to draw confirmatory conclusion. As randomization was not stratified by BMI, imbalances for baseline risk factors between treatment groups able to affect treatment outcomes cannot be excluded. Of importance, the pre-specified subgroup analysis by BMI using 18.5 kg/m^2 as cut-off did not support the conclusion of higher efficacy of anamorelin in patients with lower BMI.

6.4. Unfavourable effects

A consistent trend towards slightly higher rates of TEAEs, AESI and SAEs and in particular deaths in anamorelin treated patients in comparison with placebo in the pivotal safety population was identified. Differences observed were not very pronounced as shown by a comparison of the rates of any TEAEs (A: 78% vs. P:73.6%), SAEs (A:27.4% vs. P:26.7%) and also deaths during the 12 weeks treatment (A:12.7% vs. 10.4%).

[2] FAACT SEA is a su-bscore of FAACT A/CS, which is a subscore of FAACT TOI.

Anamorelin shows a significant arrhythmic potential due to targeting the sodium channel and has a rather narrow therapeutic range which is characterized by a non- linear PK, sensitivity to CYP3A4 inhibition, other potential drug interactions and possibly hepatic dysfunction. The thorough QT study (HT-ANAM-112) confirmed that anamorelin is blocking cardiac sodium channels and the impact of this effect on potential arrhythmias was demonstrated.

As expected considering the mechanism of action of the drug, hyperglycaemia and diabetes occurred more commonly in the anamorelin treated subjects.

The incidence of the TEAEs with PTs of increased ALT, AST, GGT, Blood Alkaline Phosphatase and Blood Bilirubin reported in Studies HT-ANAM-301 and HT-ANAM-302 and in the extension study were not associated with significant hepatic toxicity. However, taking into account the short duration of exposure to anamorelin and the potential underreporting of adverse events in these trials, the true extent of drug induced hepatotoxicity cannot be comprehensively evaluated at this stage.

In the pooled pivotal studies it is shown that the percentage of deaths after 12 months was 58.0% in the placebo group and 60.2% in the anamorelin group. Median survival time was 9.2 months for the placebo group and 8.9 months for the anamorelin group. The hazard ratio (anamorelin vs. placebo) was 1.06 (p = 0.4691). However, when patients were on anamorelin treatment (12 weeks in study 301 or 302 and 12 weeks in study 303) survival rates where in favour for anamorelin (6 months percentage of death was 63.2% for placebo and 66.1% for anamorelin).

6.5. Uncertainties and limitations about unfavourable effects

The deficiencies observed with regard to the collection and reporting of the safety data in the two inspected trials at the investigator sites raised concerns on the reliability of the safety results presented. The additional information provided by the CRO during the re-examination procedure has not alleviated these concerns.

Due to the flaws and uncertainties in the design and conduct of the clinical studies, it cannot be concluded that anamorelin is not associated with cardiac toxicity. There are signals both from the pre-clinical and clinical studies which merit further investigation to exclude the potential detrimental effects of anamorelin.

Furthermore, due to inaccurate/incomplete registration of the concomitant treatments, the impact of e.g. systemic corticosteroids use on the observed hyperglycaemia is unclear.

From a theoretical point of view stimulation of tumour growth by treatment with anamorelin could be hypothesized. Unfortunately, this issue cannot be further clarified, since the applicant has not adequately investigated this possibility.

6.6. Effects Table

Table 44. Effects Table for anamorelin in the treatment of cancer cachexia in NSCLC.

Effect	Short description	Unit	Anamorelin	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Lean Body Mass	Change from baseline measured by Dual Energy X-Ray Absorptiometry Scans	Kg	1.16 1.25	-0.37 -0.46	Small effect size of uncertain clinical relevance, no correlation with other endpoints Larger effect size in sub-population but sub-group prioritised only post-hoc	Pooled analysis of studies 301/302 Pooled analysis for of studies 301/302 in patients with a BMI <20 kg/m^2
Handgrip strength	Change of the Non-Dominant Hand from Baseline Over 12 Weeks	Kg	1.46 -1.49	0.48 -0.95	No statistical difference between placebo and anamorelin	Study 301 Study 302
Quality of Life Measures	FAACT-total score FACIT-F	N/A	6.46 2.02	3.78 -0.05	The validated QoL measures including FACIT-F and FAACT failed to show statistically significant difference from placebo.	Study 301
Unfavourable Effects						
TEAEs leading to Deaths		%	16.4	14.6	Difficult to interpret due to the frailty of the cancer patients	All cancer patients in phase II and III
Cardiac toxicity and arrhythmia	Torsade de pointes/ QT prolongation SMQ	N	3	0	Preclinical data and torough QT study appear in conflict with the observations in ROMANA-1 and 2 databases. GCP shortcomings and underreporting of AEs	All cancer patients in phase II and III
Hepatotoxicity	Drug-related hepatic disorders SMQ	%	10.6	7.3	ALT values increased indicating hepatic damage. GCP shortcomings and underreporting of AEs	All cancer patients in phase II and III

Abbreviations: ALT= Alanine transaminase, BMI= Body mass index, FAACT=functional assessment of anorexia/cachexia therapy (FACT-G + A/CS), FACIT-F=functional assessment of chronic illness therapy - fatigue (FACT-G + fatigue subscale), SMQ= Standardised MedDRA Query

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

Anamorelin has been proposed to improve cancer-related anorexia/cachexia in patients treated in a palliative setting. For the proposed target indication, acceptable goals of treatment would include demonstration of improvement in body mass associated with a clear effect on an adequately validated subjective/functional variable ensuring patient clinical relevance. An improvement in LBM on its own is not considered sufficient to support translation into clinical benefit.

The co-primary endpoint of HGS failed to show any significant difference between the two study arms. Similarly, two accepted QoL questionnaires (FAACT A/CS and FACIT-F) were not able to consistently demonstrate (clinically or statistically) benefit for the patients treated. Changes in QoL exceeding the defined MID were reported only in few of the subscales examined. The results appear to be more pronounced in the subgroup of patients with BMI <20 kg/m^2. However, the subgroup analysis in patients with BMI <20 kg/m^2 was performed post-hoc in the context of overall negative studies, due to the fact that the co-primary HGS endpoint was not met. No plausible rationale explaining why anamorelin is more effective in the identified subgroup has been provided, whereas the introduction of bias related to a data driven approach cannot be excluded. On this regard it should be noted that the pre-specified subgroup analysis by BMI using 18.5 kg/m^2 as cut-off did not support the conclusion of higher efficacy of anamorelin in patients with lower BMI. Therefore, the results can be considered only hypothesis generating and not able to support grant of marketing authorisation for this subgroup.

Further, as concomitant medication was not systematically collected the potential impact of e.g. systemic corticosteroids on weight gain could therefore not be assessed.

For the overall population, an increased toxicity is consistently demonstrated by the observed higher incidence of TEAEs, SAEs, treatment discontinuation due to TEAEs and deaths in anamorelin treated patients compared to placebo treated patients. The results of inspections performed at several study sites raise concerns over the reliability of the safety data reported. In particular, adverse events could be significantly underreported. Due to this potential underreporting, the cardiotoxicity and hepatotoxicity of anamorelin cannot be assessed thoroughly.

6.7.2. Balance of benefits and risks

For the overall population treated as well as the subgroup of patients with BMI <20 kg/m^2, the observed marginal effect on LBM without a clear and clinically relevant effect on QoL does not counterbalance the observed treatment related toxicity. This also in view of the concerns raised about the accuracy of the safety database regarding the potentially considerable under -reporting of adverse events.

6.8. Conclusions

The overall B/R of Adluiz is negative.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by consensus that the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product. The CHMP considers that:

- Given the marginal effect on LBM without showing a reliable and clinically relevant effect on patient functioning or QoL, the therapeutic efficacy of anamorelin is not established.
- Restricting the indication to the subgroup with Body Mass Index <20 kg/m^2 is not considered acceptable given that this subgroup was prioritised post-hoc and confirmatory conclusions of the benefit -risk based on this subgroup analyses cannot be made.
- There are significant concerns regarding evaluation of the safety profile of Adlumiz based on the overall small size of the clinical safety database, and in particular in light of the conclusion from the GCP inspection that the integrity of the safety database is compromised. The trends of higher morbidity and on treatment mortality rates across the clinical studies and the signals for cardiovascular events and hepatoxicity observed in pre-clinical studies with limited safety margins in relation to the doses used in human studies cannot be comprehensively evaluated.